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Single-Dose Absorption and Pharmacokinetics of WR 6026

TASK ORDER #3
FINAL REPORT

Brent G. Petty, M.D.
David M. Kornhauser, M.D.
Theresa B. Shapiro, M.D., Ph.D.
Paul S. Lieiman, M.D., Ph.D.

01 August 1988

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Division of Clinical Pharmacology
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WR 6026 (8-(6-diethylaminohexylamino)-6-methoxy-4-methylquinoline dihydrochloride) is a promising agent for the treatment of visceral leishmaniasis based on experiments in both an animal model and an in vitro test system. This human study was performed in order to increase our understanding of the pharmacokinetics, safety, and tolerance of a single oral 60 mg dose of WR 6026 in healthy male volunteers.

Eight subjects who gave written informed consent participated in this study which was conducted in the Clinical Pharmacology Research Unit, an inpatient service at the Johns Hopkins Hospital and which was approved by the Joint Committee on Clinical Investigations of The Johns Hopkins Medical Institutions and the Human Use Review Office of the U.S. Army. Following the administration of a single dose of 60 mg of WR 6026, serial blood specimens and urine collections were obtained in order to assess the pharmacokinetics of this compound. The volunteers were monitored for subjective tolerance by daily interview and for objective toxicity with clinical laboratory tests of hematology and chemistry variables,

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19 ABSTRACT (continued)

electrocardiograms, urinalysis, and methemoglobin determinations.
All of the subjects tolerated WR 6026 very well with no adverse symptoms. Two subjects had an increase in the serum aspartate aminotransferase (AST, SGOT) on the fourth day after drug administration and one had a corresponding increase in the serum alanine aminotransferase (ALT, SGPT). Four other subjects had elevations of the serum lactic dehydrogenase (LDH), three on the fourth and one on the second day following drug administration. Whether these elevations were related to laboratory variability or to a delayed effect of the drug is not clear. One subject had an increase in fasting serum triglycerides on the second day following drug administration. No subject had a significant change in hematological parameters, electrocardiograms, methemoglobin, creatine kinase or urinalysis.
The pharmacokinetic results demonstrated that there was approximately a 30-minute lag time between administration and detectable drug absorption, with peak WR 6026 concentrations occurring approximately three hours after drug administration. The areas under the plasma concentration-time curves varied approximately fourfold between the eight subjects. The data were not well described by compartmental analysis. However, using a one-compartment model the mean elimination half-time was about 11 hours, with a relatively wide range between subjects of 5.2 to 17.3 hours.
The urinary excretion of the parent drug and two metabolites over 6 days after dosing with 60 mg WR 6026 was quantified. The average amount of drug recovered in the urine as these three compounds was 14.1% of the dose of WR 6026 administered, with a range of 6.2-30.0%.
In the first two subjects, whole blood as well as plasma concentrations of WR 6026 were measured after dosing. Concentrations in whole blood were lower than those in plasma, indicating that the drug was not concentrated in the cellular components of blood.

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SUMMARY

WR 6026 (8-(6-diethylaminohexylamino)-6-methoxy-4-methylquinoline dihydrochloride) is a promising agent for the treatment of visceral leishmaniasis, based on experiments in both an animal model and an *in vitro* test system. This human study was performed in order to increase our understanding of the pharmacokinetics, safety, and tolerance of a single oral 60 mg dose of WR 6026 in healthy male volunteers.

Eight subjects, who gave written informed consent, participated in this study which was conducted in the Clinical Pharmacology Research Unit, an inpatient service at The Johns Hopkins Hospital, and which was approved by the Joint Committee on Clinical Investigations of The Johns Hopkins Medical Institutions and the Human Use Review Office of the U. S. Army. Following the administration of a single dose of 60 mg of WR 6026, serial blood specimens and urine collections were obtained in order to assess the pharmacokinetics of this compound. The volunteers were monitored for subjective tolerance by daily interview and for objective toxicity with clinical laboratory tests of hematology and chemistry variables, electrocardiograms, urinalysis, and methemoglobin determinations.

All of the subjects tolerated WR 6026 very well with no adverse symptoms. Two subjects had an increase in the serum aspartate aminotransferase (AST, SGOT) on the fourth day after drug administration and one had a corresponding increase in the serum alanine aminotransferase (ALT, SGPT). Four other subjects had elevations of the serum lactic dehydrogenase (LDH), three on the fourth and one on the second day following drug administration. Whether these elevations were related to laboratory variability or to a delayed effect

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In the first two subjects, whole blood as well as plasma concentrations of WR 6026 were measured after dosing. Concentrations in whole blood were lower than those in plasma, indicating that the drug was not concentrated in the cellular components of blood.

FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

For the protection of human subjects the investigators have adhered to the policies of applicable Federal Law 45 CFR 46.

TABLE OF CONTENTS

1. INTRODUCTION

Visceral leishmaniasis is a serious disease caused by the parasite Leishmania donovani (1). Though it is ordinarily a zoonosis transmitted between animals, especially rodents and canines through the bites of infected sandflies, humans may also be infected. It is found in parts of Europe, Africa, Asia, Central America and much of South America. The disease causes prolonged debility, and left untreated it causes death in 75% to 90% of patients. Cutaneous leishmaniasis is not lethal, but may cause substantial morbidity (1). Not only is leishmaniasis a major world health problem, it is also a problem for U.S. military forces stationed in areas where transmission of the disease occurs.

The mainstay of therapy for leishmaniasis is pentavalent antimony. To produce a cure, this must be administered in repeated doses over a period of up to one month. While side effects are rare, their incidence is dose-related. Up to 15% of patients may relapse after antimony therapy and must be given extended antimony treatment or be treated with other drugs which are toxic (2). Pentamidine causes significant side effects including fatigue, anorexia, nausea, abdominal pain and prolonged hypoglycemia. Ten percent of patients treated with this drug develop permanent diabetes. Amphotericin B causes fever, fatigue, nausea, vomiting, anemia, uremia, and thrombophlebitis. Most significantly, it also produces permanent impairment of renal function in many patients. Given the significant failure rate of antimony compounds and the toxicity of other effective drugs, there is a clear need for development of alternative drugs.

WR 6026 (8-(6-diethylaminohexylamino)-6-methoxy-4-methylquinoline

dihydrochloride) (Figure 1) has been shown to be a highly active anti-leishmanial drug, both in an animal and an in vitro test system. Like primaquine, it is an 8-aminoquinoline. In hamsters infected with L. donovani, it produced significant suppression of infection in a dose of 0.025 mg/kg administered orally twice daily for four days, making it approximately 700 times more active than the reference antimonial compound pentostam (3). In the human macrophage-L. tropica test system, it was approximately 7 times more active than pentostam (4).

Subchronic toxicity studies of WR 6026 in rats given daily oral doses of 4.5, 9 or 18 mg/kg for 28 days revealed minor changes in blood counts and serum chemistry values including minor increases in methemoglobin levels (5). Target organs identified in these studies by histopathologic examination were lung and uterus at intermediate and high doses, and spleen, heart and kidneys at high doses. The abnormalities encountered in these organs included increased numbers of alveolar macrophages and eosinophilic granular material in alveolar spaces in the lung; hydrometra in the uterus; extramedullary hematopoiesis in the spleen; myocardial fibrosis in the heart; and proteinaceous casts along with abnormalities of tubular epithelium, including necrosis, in the kidney.

Subchronic toxicity studies of WR 6026 were conducted in dogs given daily oral maintenance doses of 0.3, 1 or 3 mg/kg for 25 days after loading doses of four times the daily maintenance dose on Day 1, three times the daily maintenance dose on Day 2, and twice the daily maintenance dose on Day 3. These studies revealed no significant changes in blood counts apart from a mild decrease in platelets after the first week of dosing with subsequent

return toward pre-treatment levels, and a mild increase in reticulocyte counts at mid- and high-dose levels (6). Methemoglobin levels increased with increasing drug dose. Control dogs had methemoglobin levels of less than 1%; the mean value for low-dose dogs was 1.4%, for mid-dose dogs was 8.8% and for high-dose dogs was 35%. Serum albumin levels were decreased mildly in mid- and high-dose dogs. Mild to moderate increases were also observed in serum globulin, SGOT, LDH, cholesterol, and triglycerides, and there was a 2-3 fold increase of haptoglobin levels. These animals also developed dose-related weight loss at the mid- and high-dose levels.

Histomorphologic abnormalities in mid- and high-dose dogs were found in the liver, spleen, heart, kidney and gallbladder. In mid- and high-dose dogs, there was increased extramedullary hematopoiesis in the spleen. In spleens of high-dose dogs, there was also congestion of the red pulp, as well as plasma cell infiltration and lymphoid depletion. In addition, high-dose dogs had bile duct hyperplasia, pleocellular periportal infiltrates, and vacuolated reticuloendothelial cells in the liver. Two dogs in the high-dose group had cytoplasmic degeneration of myocardium. In the kidneys of one high-dose dog there was tubular necrosis as well as brown granular pigment in tubular cells. The gallbladder in mid- and high-dose dogs showed mucosal hyperplasia associated with inspissated bile.

In a study comparing the cardiovascular and pulmonary effects of WR 6026 and primaquine in anesthetized dogs during intravenous infusion of the drugs, the major effects of WR 6026 at infusions of 1.0, 2.5, and 4.0 micromoles/kg/min were a weakening of ventricular contractility and a constriction of the pulmonary vasculature (7). These effects were more

significant at increasing infusion rates. In addition, there was short-lived prolongation of the P-R and Q-T intervals at the higher doses. No cardiac arrhythmias were noted.

Phase I testing of WR 6026 in 44 healthy male subjects given increasing single oral doses of up to 60 mg (60 mg given to only two subjects) revealed no significant drug-related symptoms or physical or laboratory abnormalities (8). Laboratory studies designed to detect the occurrence of hemolytic anemia revealed no significant differences in comparison with subjects treated with placebo. Methemoglobinemia did not occur in any subject.

In efficacy and toxicity studies in man conducted during World War II among volunteers infected with vivax malaria (Chesson strain), WR 6026, administered in an oral dose of up to 30 mg base daily concurrently with quinine (2.0 grams salt per day) for 14 days, was associated with 2.0-3.1% methemoglobinemia, low grade leukocytosis (WBC 12,000-14,000) and non-specific T wave changes on EKG (9). No other significant drug-related side effects were noted.

The purpose of this study was to determine the pharmacokinetics, safety and tolerance of a single 60 mg dose of WR 6026 in a larger group of healthy volunteers than previously studied at this dose. These data could then be used to design appropriate multiple-dose studies.

2. MATERIALS AND METHODS

2.1 WR 6026

WR 6026 (manufacturer's code WRA-20-05186, bottle #BK01845) was supplied by the Army as 15 mg capsules and was delivered to The Johns Hopkins Hospital Adult Medicine Pharmacy. Capsules were

prepackaged by the pharmacy study monitor in unit packets containing four 15 mg capsules, labelled by dose and subject name. Each subject was administered a single 60 mg (4 x 15 mg) dose.

2.2 SUBJECTS

A group of eight healthy male volunteers capable of providing written informed consent was recruited for study participation. Institutional Review Board approval was obtained from both the Joint Committee on Clinical Investigations of The Johns Hopkins Medical Institutions and the Human Use Review Office of the U.S. Army.

2.2.1 Inclusion Criteria

Participants in this study were to be males between 18 and 35 years of age and within the Army's weight limit fo height according to AR 600-9. Subjects were required to have no clinically significant medical condition as determined by a detailed medical history and physical examination performed by a physician. Serum chemistry profile, hematology and urine analysis were required to be within the normal ranges as defined by The Johns Hopkins Hospital Department of Laboratory Medicine. Chest x-ray within six months of entry and an electrocardiogram had to be normal. Prospective volunteers were required to be available and agreeable to be confined to the Clinical Pharmacology Research Unit for the entire study period.

2.2.2 Exclusion Criteria

Women were excluded from this study. Men were excluded if they did not meet the entrance criteria listed above (2.2.1) or if

they had a known or suspected allergy to antimalarial compounds or related drugs. Candidates requiring systemic medication were not eligible for study participation. Subjects with documented glucose-6-phosphate dehydrogenase (G6PD) deficiency, determined by a quantitative assay of enzyme activity with levels less than 7.4 IU/per gram of hemoglobin, or abnormal methemoglobin levels were excluded from study participation. Once accepted as a candidate for the study, subjects were not permitted to take any medication for 72 hours prior to admission into the study.

2.2.3 Recruitment

Advertisements were placed in the Help Wanted classified sections of the metropolitan Baltimore Sun newspaper. A special telephone line was dedicated to volunteer recruitment. Interested candidates were pre-screened on the telephone by research personnel who described the details of the study, took a brief medical history, and scheduled the candidates for additional screening examinations.

2.2.4 Informed Consent

Written informed consent was obtained from each subject prior to entering the study and was made a part of the subject's permanent study record. The informed consent described in detail the purpose of the study, the research protocol, and the associated potential risk. Each subject was advised that study participation was voluntary and that he could withdraw at any time. Each subject was afforded ample opportunity to ask

questions of the investigator prior to and after entering the study.

2.2.5 Compensation

Based on the duration of time the subject stayed in the hospital and the numerous venipunctures and urine collections required during the study, subject compensation was computed at $250 per subject for completion of the study.

2.3 EXPERIMENTAL PROTOCOL

2.3.1 Objectives

The primary objective of this study was to determine the pharmacokinetics of a single oral 60 mg dose of WR 6026 in healthy adult male subjects. The information obtained from this study could then be used in the design and development of multiple-dose studies for WR 6026. Additionally, we evaluated the tolerance and toxicity of a single oral 60 mg dose of WR 6026 in these subjects.

2.3.2 Design

This study was an open-label design with each subject receiving a single 60 mg oral dose of WR 6026. The dose was given after an eight-hour fast and the subjects were allowed to resume eating four hours after the dose was given. The subjects swallowed the dose under the observation of study personnel.

The study examined each subject's tolerance of a single 60 mg dose of WR 6026 through regular, non-directed questioning regarding symptoms of adverse effects. Clinical laboratory

studies, including chemistry profiles, hematology tests, urine analysis, and methemoglobin levels, were monitored at regular intervals. Electrocardiographic measurements were also obtained at regular intervals before and after drug administration. The Study Flow Chart, showing the scheduled time of each event in the protocol, is Appendix A.

All subjects were screened as outpatients. Drug administration, blood and urine specimen collection, and post-drug tolerance and toxicity evaluations were performed during the inpatient hospital phase.

2.4 CLINICAL LABORATORY EVALUATIONS

All laboratory evaluations, with the exception of assays for WR 6026 and its metabolites, were done within The Johns Hopkins Medical Institutions. Hematology and chemistry determinations were performed by the Department of Laboratory Medicine (Clinical Laboratory License No. 19-1054). Clinical laboratory tests were conducted at screening, two days prior to drug administration, immediately before drug administration and at 24, 48 and 96 hours post-dose.

2.4.1 Hematology

Routine hematologic determinations including hematocrit, hemoglobin, red blood cell count, white blood cell count with differential count, and platelet count were done.

2.4.2 Serum Chemistry

Serum was assayed for sodium, potassium, chloride, CO_2, urea nitrogen, creatinine, glucose, uric acid, calcium, phosphate,

total protein, albumin, direct and total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactic dehydrogenase (LDH), creatine kinase (CK), and methemoglobin levels. Cholesterol and fasting triglyceride tests were done 24 hours pre-dose and at 24, 48 and 96 hours post-dose.

2.4.3 Urine Analysis

Urine analysis was performed by personnel in the Division of Clinical Pharmacology. Protein, ketones, glucose, and bilirubin were measured qualitatively, and pH and specific gravity were determined. A microscopic examination of the sediment was also performed.

2.4.4 Electrocardiography

A standard 12-lead electrocardiogram (ECG) was performed on each subject at screening, just prior to drug administration, and at 4 hours, 1 day, 2 days, and 4 days after drug administration. All ECG's were reviewed and interpreted by a physician on the staff of The Johns Hopkins Hospital in the Division of Internal Medicine.

2.4.5 Chest X-rays

Standard postero-anterior and lateral chest x-rays were performed on each subject within six months of entry into the study. All x-rays were reviewed and formal reports provided by The Johns Hopkins Hospital Department of Radiology.

2.5 SPECIMEN HANDLING

2.5.1 Blood/Plasma Collection and Storage

Venous blood specimens were collected into heparinized glass tubes using an indwelling catheter fitted with a heparin lock. Blood specimens were centrifuged for 10 minutes and the plasma was decanted into plastic storage vials and frozen at -80°C. Whole blood samples were also obtained from Subjects #1 and #2, transferred to plastic vials, and frozen at -80°C. All blood and plasma specimens were labelled with the subject's initials and number, and the date and time of collection.

2.5.2 Urine Collection and Storage

For each urine collection period (as specified by protocol), the total urine volume was carefully measured and recorded. Aliquots from each collection were stored in three 60 ml plastic containers at -80°C. All urine specimens were labelled with the subject's initials and number, and the date and time period of collection.

2.5.3 Specimen Shipment

The frozen plasma and blood specimens were shipped in a sealed insulated container packed with dry ice. Shipment was made by an overnight carrier to Dr. Emil Lin at the University of California at San Francisco. The frozen urine specimens were transported in a sealed insulated container packed with dry ice. The urine samples were picked up by Army personnel and delivered to the laboratory of Dr. Anthony Theoharides at the Division of Experimental Therapeutics at WRAIR.

2.6 ASSAY OF WR 6026 AND METABOLITES

2.6.1 Assay of WR 6026 in Plasma and Blood

Concentrations of WR 6026 in plasma were assayed according to the method utilized by Dr. Emil Lin (10). Briefly, 0.5 ml of plasma was precipitated with 1.2 ml of CH_3CN containing the internal standard WR 223658. The mixture was centrifuged and the supernatant applied to C_2 Bond Elut cartridges which had been previously washed with 3 ml of 98% CH_3CN containing 0.1% sodium lauryl sulfate (SDS), 6 ml of water and 3 ml of CH_3CN. The cartridges were washed with 2 ml of 100% CH_3CN and 1 ml of CH_3CN containing 0.1% SDS. The WR 6026 was eluted with 3 ml of 98% CH_3CN containing 0.1% SDS into silanized tubes. Eluates were evaporated to dryness under nitrogen at room temperature. The residues were reconstituted in 200 ul of 80% CH_3CN. Aliquots were chromatographed on an Altex C_8 column using a mobile phase of acetonitrile:water (60:40) containing 0.2% SDS (wt/vol) and 0.2% glacial acetic acid (vol/vol) with the final volume adjusted to pH 5.5 with ammonium sodium lauryl sulfate hydroxide at a flow rate of 1.2 ml/min. Drug was detected by measuring absorbance at 263 nanometers.

The assay had a level of detection for the WR 6026 base of 6.44 ng/ml. The desethyl metabolite of WR 6026 (8-(6-ethylamino-hexylamino)-6-methoxy-4-methylquinoline dihydrochloride hemihydrate--WR 211789) can also be quantitated with this same method with a quantitation limit of 8.0 ng/ml. Precision of the assay, measured as the percent coefficient of variation of replicate spiked samples of WR 6026 in plasma, varied from

1.23% to 5.10% for inter-day and 2.78 to 10.2% intra-day analysis (10). Blood was also assayed, although the procedure was not validated. One-half ml of water was added to 0.5 ml of blood. The mixture was vortexed and then 1.2 ml of CH_3CN containing the internal standard and 1.0 ml of CH_3CN were added. The resultant mixture was vortexed for 20 seconds, sonicated for 10 minutes and centrifuged. The supernatant was treated identically to the plasma supernatants (10). Results of the analysis of blood samples must be regarded as preliminary since the method was not validated at the time the assays were performed.

2.6.2 Assay of WR 6026 and its Metabolites in Urine

Urine was assayed for WR 6026 and its desethyl (WR 211789) and 4-hydroxymethyl (8-(6-diethylaminohexylamino)-6-methoxy-4-hydroxymethylquinoline dihydrochloride hydrate--WR 254421) metabolites by Dr. Anthony Theoharides, Department of Pharmacology, Division of Experimental Therapeutics at WRAIR. The assay is detailed in his report (11). Briefly, the internal standard, WR 223658, was added to ten ml of urine. The mixture was applied to Baker 3 ml silica gel solid phase extraction columns which had been prewashed with 6 ml each of deionized water, methanol and deionized water. The columns were washed with 6 ml of 50% ethanol/deionized water. The compounds of interest were eluted with 6 ml of 50% ethanol/0.1M ammonium acetate, pH 7.5, into clean extraction tubes and evaporated to dryness under nitrogen at 35°C. The residue was reconstituted in 200 microliters of methanol and

analyzed by HPLC.

Chromatography was performed using a 10 micron micro bond pack C-18 steel column from Water Associates with electrochemical detection using a glassy carbon electrode operated in the oxidative mode at an applied potential of +0.80 volts (Model TL-6A, BAS). The mobile phase used for the chromatography was 0.1M ammonium acetate, pH 4.5:acetonitrile (68:32) at a flow rate of 1.5 ml/minute. The method is accurate to within 7% for each of the three compounds, while the coefficients of variation range from 7% to 27%, depending upon both the compound and the concentration (11).

2.7 PHARMACOKINETIC ANALYSIS

Visual analysis of plots of the concentration of WR 6026 against time demonstrated that after a short lag period, plasma concentrations of WR 6026 rose and then gradually declined. In most subjects, the data appeared to be most consistent with a one-compartment model with first-order absorption following a time lag for absorption to begin, and with first-order elimination. In some instances, the last one or two measured concentrations appeared to lie above the expected concentrations if a single elimination phase were present, suggesting the possibility of biphasic elimination. PC NONLIN^{R}, a commercially available curve fitting program (12), was used to estimate the pharmacokinetic parameters for each patient assuming a single compartment with first-order absorption after a time lag and first-order elimination. Analyses of the data from several patients were performed weighting the concentration at each time point equally.

This method estimated poorly the low plasma concentrations, i.e., those occurring early after dosing and those greater than 24 hours after dosing. Accordingly, analyses were performed which weighted the data proportionally to the inverse of the square of the concentration. This technique provided better estimates of both low and high plasma concentrations. However, the peak concentrations were consistently underestimated. A two-compartment model was tried to see whether the data could be fit better with this model. Using this model, peak concentrations were estimated poorly, and the standard errors of the parameter estimates were very large, suggesting that there were insufficient data for the model. Attempts were made to fit the data to a two-compartment model with MK MODEL^{R}, another commercial curve-fitting program (13). Large standard errors of the estimates were obtained using this program as well. RSTRIP^{R}, a pharmacokinetic data stripping program with least squares parameter optimization (14), was also tried. RSTRIP^{R} produced parameter estimates to approximate the data with equations containing two and three exponential terms (equivalent to one- and two-compartment models with first-order absorption). Once again, error estimates of the variables were large for the two-compartment fits, indicating that the data were insufficient to describe a model of this complexity. Accordingly, PC NONLIN^{R} was used to fit the plasma and blood concentrations to a one-compartment model with data weighted to the inverse square of the concentration since this model provided the best approximation of the observed data. The amounts of WR 6026 excreted into the urine unchanged were used to estimate the elimination rate constant of WR 6026 from the plasma. WR 6026 was

not detected in the urine collected from 84 to 96 hours after dosing except in Subject #5, in whom less than 2% of the total drug excreted unchanged was present. This suggested that the excretion of unchanged drug was complete at the end of the collection period. The natural logarithm of the amount of unchanged drug remaining to be excreted ($X_U^\infty - X_U^t$) was plotted against time (15). Unweighted linear regressions were performed to estimate the slope of the line, which is equal to the negative of the elimination rate constant of WR 6026 from the plasma.

The single exponential decline of the plot of the urinary data suggested that all the data, the amount of unchanged WR 6026 excreted in the urine and the plasma concentrations of WR 6026, could be used together to model the pharmacokinetics of WR 6026. PC NONLIN^R was used to estimate the parameters of a one-compartment model with first-order absorption after a lag time and first-order elimination (including both urinary excretion and metabolism) which best described the plasma concentrations and urinary excretion of WR 6026 for each subject. Estimates were obtained when weighting each observation equally and also using the reciprocals of the observations and the reciprocals of the square of the observations as the weights for each data point.

3. RESULTS AND DISCUSSION

3.1 AMENDMENTS AND COMPLIANCE

3.1.1 Amendments

The consent form was amended prior to enrolling subjects to provide information concerning:

1. The fact that WR 6026 is not currently licensed.
2. Follow-up on significant changes in clinical laboratory tests.
3. The risks of a heparin lock.
4. The right of Army inspectors to review relevant records.
5. The treatment of any injuries incurred in this project.

The amended consent form is provided as Appendix B.

The original protocol scheduled clinical chemistry and hematology evaluations at screening, on admission to the hospital (Day 1) and on Days 4, 5, and 6. In reviewing this schedule we realized that we did not have measurements immediately prior to WR 6026 administration to use for comparison with the post-drug samples, and therefore added a zero time point for a more reliable baseline. There was a discrepancy between the text of the protocol and the flow sheet regarding the timing of CK measurements. We decided, after conferring with Army personnel, that CK should be measured at screening and at time points specified on the flow sheet.

In the original protocol the repeated urine analyses eliminated some urine from the timed collections. For this reason we stopped doing urine analyses after drug administration until the final urine collection was completed. This change was made while the second volunteer was in the midst of the protocol. Therefore, urine analyses were done per original protocol on the first subject. The second volunteer had a urine analysis on Day 4, but not on Day 5.

Eliminating the urine analysis scheduled for Days 4 and 5 allowed us to keep the continuous sequential urine collections intact after WR 6026 administration without sacrificing even a small part for urine analysis. We obtained a urine analysis after the final 12-hour urine collection was completed on Day 7 for safety data.

The lipid profile was changed from Day 2 to zero hour on Day 3. This was only a time change, and still occurred prior to drug administration.

It was initially intended to measure WR 6026 concentration in whole blood and plasma in all of our subjects. However, whole blood samples, in addition to plasma and urine, were obtained and saved only from the first two subjects. At the request of Army representatives, only plasma and urine specimens were collected for WR 6026 concentration from the remainder of our subjects.

All of the amendments mentioned above were authorized by Army personnel prior to implementation.

3.1.2 Compliance

Subjects were enrolled into the study even if screening and/or admission CK and triglyceride levels were elevated. We believe the CK elevations do not reflect a myopathic process, but rather the active physical lifestyles of the subjects. Creatine kinase levels increase with exercise, and athletes have been reported to have higher baseline levels of serum CK as their "normal" (16-23). The elevated triglyceride levels

were not far enough above the "normal range" to be considered significant. We are satisfied that these subjects were healthy and that those with elevated CK and triglycerides did not have a pathological process.

One subject (#5) who was entered into the protocol exceeded the AR 600-9 weight limit for height. He was 27 years old, 6'5" tall and weighed 231 pounds. The upper limit according to AR 600-9 for individuals age 26-39 of that height is 229 pounds. Another weight criterion often used in our healthy volunteer studies is that subjects must be within 10% of the ideal body weight specified by the Metropolitan Life Insurance table. Our Subject #5 did fall within 10% of his ideal body weight for height as listed in that table. Furthermore, this individual was very large and well-muscled, and his "excessive weight" was not due to obesity.

Three subjects were discharged but not recalled when the discharge laboratory tests returned showing that the LDH had risen above the upper limit of normal. In two of these individuals the elevation was deemed trivial and not pursued. In the other subject the LDH had risen to nearly twice the upper limit of normal. Although the subject was asymptomatic and this was an isolated abnormality in his clinical laboratory tests, the test should have been repeated and our failure to repeat the test after discharge was an oversight and deviation from the protocol.

3.2 DESCRIPTION OF SUBJECT POPULATION

During the volunteer recruitment period, 49 men responded to the newspaper advertisements. Of these, 6 failed to keep scheduled appointments, while 32 were disqualified for not meeting one or more of the inclusion/exclusion criteria. Eleven subjects were examined by the physician and qualified for study participation. Three of these were extras and were not used. The study group was comprised of eight healthy black males. The average age was 26.3 years, ranging from 20 to 34 years. The average height and weight for the study group were 179.4 cm (range 165-195) and 75.5 kg (range 54.5-105), respectively. Relevant characteristics for individual subjects are presented in Table 1.

3.3 CLINICAL RESULTS

3.3.1 Symptomatic

All of the volunteers tolerated the administration of WR 6026 very well. There were no symptomatic complaints.

3.3.2 Laboratory (Table 2)

3.3.2.1 Liver Function Tests

Two subjects had an increase in serum AST to a level less than twice the upper limit of normal on post-drug day 4, having had normal levels at each time tested prior to that day. These elevations were not associated with symptoms and only one of the two had a corresponding increase in serum ALT on the same day. In both of these subjects the subsequent serum AST levels on days 5 and 7 were within normal limits.

Two other subjects had a minimal elevation of AST or ALT (less than twice the upper limit of normal) just before the drug was administered, even though the screening levels had been normal. In these two cases the transferases remained minimally elevated, but because the initial elevation preceded the administration of the drug it was not attributable to a drug effect. There were no elevations in alkaline phosphatase. Four subjects had increases in LDH above the normal limit, three just slightly over the upper limit of normal and one reaching nearly twice the upper limit of normal. Three of the elevations were noted on post-drug day 4, while the other was present on post-drug day 2 and was back within the normal range on post-drug day 4. These modest LDH elevations were unassociated with symptoms. Inasmuch as these LDH and transferase elevations were rather mild and usually occurred four days after drug administration, it is not clear whether they were related to the drug or whether this simply represented laboratory variability. Because the elevations were an isolated finding and unassociated with symptoms, or were only slightly elevated, no follow-up blood tests for LDH were performed in the three subjects whose levels were increased on the day of discharge.

3.3.2.2 Creatine Kinase

Several of the subjects had an elevated CK at

screening and at entry into the hospital, but in no case did the CK level increase after the administration of WR 6026 to a level higher than the admission value. This is consistent with previous experience in our subjects, where CK was found to be elevated with no symptoms whatever, and, as mentioned in 3.1.2, probably represents release of this enzyme from muscle tissues as a result of a very active, physical life style rather than from a myopathic process.

3.3.2.3 Triglycerides

Only one subject developed an increase in measured serum triglycerides above the upper limit of normal. This was on the second day following drug administration. Because of a laboratory instrument malfunction, the test was not repeated on the fourth day following drug administration.

3.3.2.4 Hematological Tests

No subject had a significant change in hematocrit, white blood count, differential count or platelet count during the study period following administration of WR 6026.

3.3.2.5 Electrocardiograms

Electrocardiograms in these subjects did not show a significant change at four hours after dosing (presumably near maximum plasma levels) or during the

period of four days after drug administration. Minor, usually non-specific abnormalities were sometimes present prior to drug administration; non-specific T-wave changes developed in two subjects after drug administration, possibly attributable to lead placement in one of the two. In neither case was the magnitude of change felt to be of any significance. Furthermore, there were no symptoms of cardiac dysfunction.

3.3.2.6 Methemoglobin

No subject in this study had an increase in methemoglobin above the normal range for our laboratory after administration of WR 6026.

3.3.3 Clinical Conclusions

The subjects appeared to tolerate the administration of WR 6026 very well. No symptoms whatever were reported and none of the minimal abnormalities of the serum chemistries noted above were of clinical significance. We believe that the single dose of WR 6026 was well tolerated and that further testing can be pursued. Nevertheless, during future studies it is important to continue close monitoring of the liver function tests, triglycerides, LDH, methemoglobin and electrocardiograms, not only by virtue of the minimal abnormalities seen in this project, but also because of good clinical research practice and the experience in laboratory animals.

3.4 PHARMACOKINETIC RESULTS AND DISCUSSION

The plasma and blood concentrations of WR 6026 measured in each of the subjects at each sampling time are listed in Appendix C (10). The plasma concentrations also are tabulated according to the scheduled time of sampling in Table 3. The excretion of the parent drug and two metabolites, 4-OH WR 6026 (WR 254421) and desethyl WR 6026 (WR 211789) into the urine was quantified in the eight subjects by Dr. Theoharides at WRAIR (11). Tables copied from his report are contained in Appendix D of this report. Table 1 of Appendix D details the accuracy and precision of the assays for WR 254421, WR 211789, and WR 6026 in urine. Tables 2, 3 and 4 of Appendix D list the concentrations in each urinary sample, the volume of each sample and the amount excreted in each time period. All of the clinical results and drug concentrations for each subject are included in the Case Report Forms provided in Appendix E.

Plasma concentrations of WR 6026 measured in the eight subjects, as well as simple descriptive summary statistics, are listed in Table 3. Plasma concentrations remained below the minimal detectable concentration of 6.44 ng base/ml for a variable period of time after dosing and then rose gradually before declining. In one subject, #5, drug was not measurable until the 1.25 hour sample, while in five of the subjects drug was measurable at 0.5 hours. The time at which the peak concentration occurred also varied, ranging from 1.5 to 5.0 hours, with the average being 3.0 hours (Table 4). Peak concentrations varied from 52.5 to 116.0 ng/ml with a mean of 73.5 ng/ml. After peaking, concentrations fell gradually. Plasma concentrations remained above the minimum detectable level at 24 hours in seven sub-

jects; in two, #6 and #7, drug was still measurable at 48 hours (Table 3). Drug was not measurable in the plasma of any of the subjects 60 hours after dosing or later. Graphs of the plasma concentrations in the individual subjects are provided in Figures 2-4.

The average WR 6026 plasma concentration at each sampling time is listed in Table 3 and shown in Figure 5. The average concentration rose slowly after a short lag time. A plateau was reached at about 60 ng/ml lasting from two hours after dosing until five hours after dosing before drug levels declined. Of note, no desethyl WR 6026 was detected in the plasma specimens (10).

Whole blood as well as plasma concentrations of WR 6026 were measured after dosing Subjects #1 and #2 and are listed in Appendix C. No statistics have been calculated since values were obtained in only two subjects. Concentrations in blood were lower than those in plasma (Figure 6 compared to Figure 2) indicating that the concentration of drug in the cellular components of blood, primarily red cells, is lower than the concentration of drug in the plasma. Concentrations in both were low, only nanograms per milliliter, after a 60 mg dose, suggesting that one or more of the following occurs: poor absorption, widespread distribution, or presystemic elimination. The data were insufficient to distinguish among these possibilities.

The fraction of the dose of WR 6026 recovered in the urine in 96 hours as unchanged drug was small and variable between subjects (Table 5). Hydroxymethyl WR 6026 (WR 254421) and desethyl WR 6026 were also recovered in the urine (Table 5). In each subject, more hydroxymethyl WR 6026 was recovered than WR 6026, which in turn was

more than the amount of desethyl WR 6026. In fact, of the total amount of drug recovered as these three moieties, 76 to 96% was recovered as hydroxymethyl WR 6026. There was at least a fivefold variation in the total amount of each compound (in micromoles) excreted in the urine in 96 hours. In addition, the amounts of these compounds present in the urine collected 84 to 96 hours after dosing were small, indicating that an insignificant amount of these compounds remained to be excreted; i.e., urinary excretion was virtually complete by 96 hours. The mean fraction of the dose recovered as unchanged drug and the two metabolites was 0.141 with a standard deviation of 0.075. Recovery ranged from 6.2 to 30.0 percent of the dose (Table 5). Thus, the majority of the administered drug cannot be accounted for by the drug and the two metabolites measured in the urine in the 96 hours after dosing.

A standard pharmacokinetic model which produced good estimates of the observed plasma data could not be found. Although the rise of plasma concentrations to a peak followed by a decline suggested a one-compartment model with first-order absorption and elimination, this model did not accurately estimate the peak plasma concentrations. Changes in the weighting of the data failed to correct severe under-estimates of the peak concentrations, although when the data were weighted to the inverse square of the concentrations, the low concentrations were estimated rather well. A two-compartment model did not describe the data better; large standard errors of the model's parameter estimates were obtained, suggesting that an insufficient number of data points were present to describe the model. Therefore, a one-compartment model with data weighted to the inverse square of

the concentration was used to describe the data, realizing that the difficulties in measuring low concentrations of drug (those less than 6.4 ng/ml) and in estimating peak values serve to produce pharmacokinetic constants for each patient that are, at best, approximate. The pharmacokinetic constants do, however, provide a way to discuss quantitatively the pharmacokinetic processes and the inter-subject differences. The measured concentrations and the plasma concentrations predicted by the curve-fitting process for each subject are shown in Figures 7 through 14.

Measured peak plasma concentrations are tabulated in Table 4 while the estimates of the peaks derived from the curve fitting are listed in Table 6. The measured maximum concentrations varied by a factor of two in the eight subjects. The observed peaks were severely underestimated by the model. Furthermore, the calculated times to peak did not agree with the times at which the maximum concentrations of WR 6026 were actually observed.

The areas under the plasma concentration-time curve (AUC) also varied widely between subjects (Table 7). As measured by the trapezoidal rule, there was a fourfold difference in the AUC in the eight subjects; the mean AUC was 1066 ng·hr/ml with a range of 512 to 2179 ng·hr/ml. The coefficient of variation was 0.47. The curve fitting process produced areas under the concentration-time curves which closely approximated those obtained by the trapezoidal rule (Table 7). In 7 of the 8 subjects, the estimate of the area under the concentration-time curve was within 5% of the value calculated by trapezoidal rule. In the other subject, #8, a 12% difference

occurred.

The model parameters estimated from the plasma data are listed in Table 4. Each parameter had at least a twofold range in the eight subjects; coefficients of variation for the mean estimates were 27% to 57%. The average time before absorption was initiated was 0.55 hours with a standard deviation of 0.26 hours. The time to onset of absorption varied from 0.30 to 0.89 hours (Table 4). The mean rate constant for drug absorption was 0.88/hour with a coefficient of variation of 0.40; estimates ranged from 0.44/hour to 1.36/hour. These extremes are equivalent to calculated absorption half-times of 1.56 and 0.51 hours, respectively (Tables 4 and 6).

Estimates of the rate at which WR 6026 disappeared from the plasma also differed between subjects. The mean rate constant of elimination, K10, was 0.082/hr with coefficient of variation of 0.57. The greatest elimination rate constant was 0.192/hour in Subject #2, equivalent to an elimination half-time of 3.61 hours, while the slowest elimination occurred in Subject #3; his rate constant of elimination was 0.048/hour which translates to an elimination half-life of 14.52 hours (Tables 4 and 6).

Analysis of the data on unchanged WR 6026 in the urine provided another way of estimating the rate of elimination of WR 6026 from the plasma. Although the amount of unchanged WR 6026 recovered in the urine was small, ranging from 0.53 to 4.57 micromoles, or 0.4% to 3.2% of the administered dose, the time course of excretion was used to estimate the rate constant of elimination of WR 6026 from the plasma. The "amount of drug remaining to be excreted in the urine"

method was used to estimate the elimination rate constant, K10, and the half-life of WR 6026 in each subject. The plot demonstrated a single exponential decline, providing only the terminal elimination rate constant. The values obtained for each subject and the summary statistics are listed in Table 8. The rate constants are smaller and the half-lives longer than the estimates obtained from the modeling of the plasma concentration data in each subject except for Subject #7. Nearly a threefold variation in the parameter estimates occurred in the eight subjects. The mean rate constant of elimination, estimated from the urinary data, is 0.060/hour compared to the mean estimate of 0.082/hour from the plasma data. The mean (geometric) WR 6026 half-life is 11.6 hours when using the urinary data and 8.4 hours when estimated from the plasma concentration data.

The plasma and urine WR 6026 concentration data in combination were then used to estimate the parameters for the one-compartment model. Since the magnitude of the amounts of drug in the urine was higher than the plasma concentrations, three different methods for weighting the observed data were tried. Data were weighted equally (wt = 0), to the reciprocal of the value (wt = -1), and to the square of the reciprocal (wt = -2). The parameter estimates for the one-compartment model are displayed in Table 9 (in conjunction with the estimates obtained from the plasma data and from the urine data alone). Each method of weighting estimated the total amount of the drug recovered in the urine accurately (Table 9) as well as the time course of urinary excretion (see Figure 15 for example of fit). However, all three consistently underestimated the peak plasma concentrations. Using equal weights for each observation produced

the highest estimates of the peaks. These, however, were still much lower than the observed peaks (Table 9). Furthermore, the low concentrations were estimated least well with this weighting technique (see Figure 15), and the calculated areas under the plasma concentration-time curve had the greatest deviation from the areas under the concentration-time curve calculated with the trapezoidal rule using the plasma concentration data with extrapolation to infinite time by dividing the last measurable concentration by the estimate of the elimination rate constant (Table 9). The best estimates of the low concentrations were produced by weighting each observation by the square of its reciprocal (see Figure 15 for example); calculated areas generally were in good agreement with the areas determined by trapezoidal rule (Table 9). The observed data and calculated estimates using this "wt = -2" method are depicted in Figures 16 through 23.

As indicated in Table 9, using a one-compartment model and weighting each data point by the square of its reciprocal produced estimates of the area under the concentration-time curve which were within 10% of the AUC calculated using the trapezoidal rule. In addition, the model estimated accurately the amount of WR 6026 excreted unchanged into the urine.

The pharmacokinetic parameter estimates for the one-compartment model for each subject and the summary statistics are listed in Table 10. The calculated maximum concentrations and the calculated times at which the maximum concentration occurs differed widely from the measured peak concentrations and the times these peaks were actually

observed (Table 9). The plots of the measured plasma concentrations and the estimated concentrations demonstrate large discrepancies near the time when the peak occurred, while both the initial rise in the concentration and the later declines in concentration appear to be estimated quite closely. This suggests that the one-compartment model is not sufficiently complex to describe the late absorption of WR 6026 and its distribution throughout the subject. The mean estimates of the absorption rate constant, K10, time before onset of absorption, TLAG, and volume of distribution divided by the bioavailability, VOLUME/F, are similar to those obtained using only the plasma data (Table 4). As before, estimates of each parameter varied widely among the eight subjects.

The elimination rate constants (K10) obtained with the "weight = -2" procedure were similar to those obtained using the urinary data alone (Table 9) and were smaller than the estimates obtained from the plasma data alone in seven of the eight subjects. The mean rate constant of elimination, estimated using plasma and urinary data together, was 0.065/hour, equivalent to an elimination half-life of 10.7 hours. Six subjects had half-lives longer than 10 hours; the other two eliminated drug more rapidly. There was a threefold difference between the smallest and largest estimate. The plasma concentrations at 24 hours and later and the amounts of WR 6026 excreted into the urine for each subject are estimated closely by the individual K10's, suggesting that the terminal rate of elimination of WR 6026 from the body is described well by the model, in contradistinction to the late absorptive and distributive phases.

Thus, in the eight subjects studied, WR 6026 absorption began after a modest delay which averaged about 0.4 hours and proceeded slowly. Peak drug concentrations were not reached until 1.5 to 5 hours after dosing and drug was eliminated with a mean half-life of about 10.7 hours. Inter-subject differences in both the absorption and elimination rates resulted in large variations in the peak concentrations achieved and in the areas under the concentration-time curves. The parameter estimates, based on a compartmental analysis of the data, must be interpreted loosely since the compartment model did not accurately quantify the late absorption and early disposition, i.e., distribution, of the drug. Peak plasma concentrations were systematically underestimated by the model, suggesting that the absorption rate may be more rapid than estimated and that a rapid, distribution phase may be present as well. The sensitivity of the plasma assay limited the number of data points obtained at late sampling times, precluding analysis using a more complicated model. However, hints of a slow, terminal elimination phase appeared in the lowest concentrations measured. The simple model employed did estimate accurately the area under the plasma concentration-time curve, plasma concentrations after 24 hours and the amount of WR 6026 excreted into the urine unchanged.

Quantification of the amounts of parent drug and of two metabolites excreted in the urine over 96 hours accounted for a minor fraction of the administered oral dosage. Incomplete absorption, non-renal elimination or the presence of other metabolites, not measured using the techniques employed in this study, could account for the low

recovery of drug in the urine.

4. CONCLUSIONS

The eight volunteers studied in this project tolerated a single oral dose of 60 mg of WR 6026 very well with no symptomatic complaints. Only minimal and clinically insignificant changes in the serum chemistries were noted. Detectable WR 6026 absorption was delayed for a short period of time, about one-half hour, and proceeded slowly; peak concentrations occurred at about three hours, and varied by more than twofold in just 8 subjects. There was approximately a fourfold variability in the areas under the concentration-time curves. Compartmental analyses of the data were not optimal, but suggested that the terminal elimination half-life averaged about 11 hours and might be longer if a more sensitive assay were available.

These data suggest that further evaluation of WR 6026 in human subjects is appropriate. We believe that the next step should be multiple-dose testing in healthy subjects with close monitoring of symptoms, clinical laboratory tests, and plasma and urine concentrations of drug. Dosing once a day, or about every two half-lives, would appear to be a reasonable approach. Higher plasma levels which might be achieved during a multiple-dose investigation and later sampling times would enable a more accurate determination of the pharmacokinetics of the compound. In particular, a multiple-dose study could determine whether a single-compartment model is sufficient to describe the data or whether a slower elimination phase is present which would lead to accumulation of drug if the dosing schedule were once every one or 1.5 half-lives. In addition, further studies on the metabolism of WR 6026 should be performed, addressing two issues in

particular: (1) whether a metabolite of the parent drug--possibly 4-OH WR 6026--is present in significant amounts in plasma, and (2) the identification of the fate of the administered drug, approximately 85% of which was not accounted for in the present investigation. Possibilities which need to be examined include determining whether other as yet unidentified metabolites are excreted in the urine, such as glucuronides of either the 4-OH or desethyl metabolites, and whether there is significant loss of drug in the gastrointestinal tract.

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TABLE 1

Individual Subject Characteristics

Subject No.	I.D.	Age	Race	HT (cm)	WT (kg)	PPD*	EtOH**
01	E-W	22	B	176.0	73.0	0.5	3
02	RLH	28	B	178.0	73.6	0.5	0
03	W-F	31	B	188.0	94.0	0.5	0.5
04	LMH	24	B	165.0	54.5	0.5	3.5
05	DLA	27	B	195.0	105.0	0.5	0
06	M-P	20	B	176.0	70.5	0.5	0
07	AID	24	B	179.5	57.5	1.0	49
08	CLH	34	B	178.0	76.0	0.5	6
	MEAN	26.3		179.4	75.5		
	(± SD)	4.7		8.9	17.0		

* Average packs of cigarettes smoked per day (from subject's history)

**Ounces of alcohol per week (from subject's history)

TABLE 2

Peak Clinical Laboratory Abnormalities Developing

After WR 6026 Administration

(number in parenthesis indicates onset of abnormality in days after drug administration)*

[number in brackets indicates value just before drug administration]

Subject #	AST (units/l)	ALT (units/l)	LDH (units/l)	Trig. (mg/dl)	T wave changes
1			217 (4) [150]		(0)
2			394 (4) [145]		
3	41 (4) [23]		201 (4) [147]		
4					(1)
5		44 (0)** [39]	203 (2) [138]		
6	53 (4) [18]	49 (4) [14]		255 (2) [86]	
7	57 (0)** [37]	63 (2) [28]			
8					

Normal ranges: AST 0-35 units/l

ALT 0-30 units/l

LDH 0-200 units/l

Triglycerides 20-190 mg/dl

* The peak abnormality did not always occur on the day of onset of the abnormality.

** These two subjects were normal at screening but had slight transferase elevations on the morning blood sample taken just before drug administration.

Table 3

PLASMA CONCENTRATIONS (in ng free base/ml) OF WR6026 IN 8 VOLUNTEERS AFTER A SINGLE 60 MG ORAL DOSE

	SCHEDULED TIME OF SAMPLE (HOURS AFTER DOSING)											
	0.00	0.25	0.50	0.75	1.00	1.25	1.50	2.00	2.50	3.00	3.50	4.00
SUBJ												
1					8.23	29.80	26.80	48.70	51.00	53.10	57.20	49.20
2			7.26	30.50	50.90	60.30	75.40	56.30	67.00	59.40	69.50	59.80
3					7.47	13.00	14.70	28.90	46.80	52.50	36.60	48.30
4			12.90	18.00	37.80	51.20	59.60	82.60	85.60	68.60	68.30	62.80
5						10.60	19.40	24.90	23.20	48.90	53.30	63.40
6			8.58	13.70	24.00	29.40	31.60	49.00	42.90	62.30	54.50	60.40
7			7.17	14.40	35.90	73.20	85.70	116.00	102.00	94.10	94.90	102.00
8			7.63	13.20	14.20	16.30	45.30	65.20	60.50	64.40	47.30	66.90
#	0	0	5	5	7	8	8	8	8	8	8	8
MEAN			8.71	17.96	25.50	35.48	44.81	58.95	59.88	62.91	60.20	64.10
SD			2.41	7.26	16.62	23.44	26.40	29.58	24.99	14.25	17.60	16.69
CV(%)			27.66	40.41	65.19	66.09	58.91	50.19	41.73	22.65	29.24	26.04
MAX			12.90	30.50	50.90	73.20	85.70	116.00	102.00	94.10	94.90	102.00
MIN			7.17	13.20	7.47	10.60	14.70	24.90	23.20	48.90	36.60	48.30

	SCHEDULED TIME OF SAMPLE (HOURS AFTER DOSING)											
	5.00	6.00	8.00	10.00	12.00	24.00	36.00	48.00	60.00	72.00	84.00	96.00
SUBJ												
1	44.40	45.90	31.40	32.30	19.70	9.80						
2	57.90	36.10	24.80	21.50	11.40							
3	46.60	39.20	33.60	32.50	26.90	15.00	12.00					
4	75.50	52.40	36.80	37.20	24.10	17.60	8.79					
5	72.00	60.10	47.20	38.30	32.70	12.00	7.67					
6	50.50	50.20	38.50	32.60	30.20	13.40	10.40	7.73				
7	91.40	89.70	88.40	64.60	66.00	31.00	17.00	11.30				
8	62.00	54.20	30.80	27.60	19.70	8.43	6.60					
#	8	8	8	8	8	7	6	2	0	0	0	0
MEAN	62.54	53.48	41.44	35.83	28.84	15.32	10.41	9.52				
SD	16.21	16.61	20.07	12.78	16.45	7.57	3.76	2.52				
CV(%)	25.93	31.06	48.45	35.66	57.06	49.42	36.10	26.53				
MAX	91.40	89.70	88.40	64.60	66.00	31.00	17.00	11.30				
MIN	44.40	36.10	24.80	21.50	11.40	8.43	6.60	7.73				

Absent values indicate the concentration was less than the minimum detectable concentration of 6.44 ng/ml

Table 4

Pharmacokinetic Parameters for Individual Subjects

PLASMA

SUBJ	VOLUME/F[1] L	K01[2] /HR	K10[3] /HR	TLAG[4] HR	AUC[5] NG.HR/ML	PEAK CONC[6] NG/ML	PEAK TIME[7] HR
1	813.98	1.36	0.088	0.89	692.34	57.2	3.5
2	512.19	1.32	0.192	0.44	503.01	75.4	1.5
3	1013.90	0.72	0.048	0.79	1022.39	52.5	3.0
4	693.06	1.15	0.067	0.36	1073.80	85.6	2.5
5	699.09	0.44	0.076	0.88	930.48	72.0	5.0
6	875.82	0.83	0.051	0.32	1114.84	62.3	3.0
7	416.34	0.63	0.055	0.42	2141.96	116.0	2.0
8	843.59	0.58	0.081	0.30	722.71	66.9	3.8
MEAN	733.50	0.88	0.082	0.55	1025.19	73.5	3.0
SD	196.35	0.35	0.047	0.26	498.79	20.1	1.1
CV(%)	26.77	39.77	56.736	46.74	48.65	27.4	36.0
MAX	1013.90	1.36	0.192	0.89	2141.96	116.0	5.0
MIN	416.34	0.45	0.048	0.30	503.01	52.5	1.5

BLOOD

SUBJ	VOLUME/F L	K01 /HR	K10 /HR	TLAG HR	AUC NG.HR/ML	PEAK CONC NG/ML	PEAK TIME HR
1	1239.19	1.90	0.066	0.88	603.70	39.1	3.5
2	782.04	1.20	0.170	0.30	372.14	60.9	1.5

1 Volume of distribution divided by fraction available, F
2 Absorption rate constant
3 Elimination rate constant
4 Time delay before onset of absorption
5 Area under the concentration time curve for the equation fit to the plasma concentrations
6 Observed peak plasma concentration, as free base
7 Time at which peak concentration occurred

Table 5

Recovery of WR6026 in the Urine as Unchanged Drug and Metabolites[1]

	Hydroxymethyl-WR6026 (micromoles)	Desethyl WR6026 (micromoles)	WR6026 (micromoles)	Total Recovered (micromoles)	% Dose Recovered
Subj					
1	24.5	0.25	0.82	25.6	17.7
2	14.0	0.22	0.57	14.8	10.3
3	17.2	0.29	1.56	19.0	13.1
4	7.9	0.18	0.87	9.0	6.2
5	9.8	0.14	0.53	10.5	7.3
6	16.9	0.26	1.33	18.5	12.8
7	17.6	0.79	4.57	23.0	15.9
8	41.3	0.52	1.47	43.3	30.0
MEAN	18.7	0.3	1.5	20.5	14..
STD. DEV.	10.5	0.2	1.3	10.8	7.5

[1] Each subject received a 60 mg dose of WR6026 dihydrochloride, which is 144.6 micromoles.

Table 6

Derived Pharmacokinetic Parameters for Individual Subjects

PLASMA

SUBJ	KO1 HL[1] HR	K10 HL[2] HR	TMAX[3] HR	CMAX[4] NG/ML
1	0.51	7.89	3.04	50.33
2	0.53	3.61	2.15	69.55
3	0.96	14.52	4.82	40.27
4	0.60	10.42	2.99	59.94
5	1.56	9.11	5.67	49.18
6	0.84	13.67	3.91	47.11
7	1.09	12.49	4.63	94.10
8	1.20	8.54	4.25	42.59
MEAN	0.91	8.43[5]	3.93	56.63
SD	0.37		1.15	17.86
CV(%)	40.36	35.44	29.26	31.53
MAX	1.56	14.52	5.67	94.10
MIN	0.51	3.61	2.15	40.27

BLOOD

SUBJ	KO1 HL HR	K10 HL HR	TMAX HR	CMAX NG/ML
1	0.37	10.48	2.72	35.38
2	0.58	4.08	2.20	45.80

1 Absorption halflife
2 Elimination halflife
3 Time at which maximum concentration occurs according to fitted equation
4 Maximum concentration from fitted equation
5 Geometric mean.

Table 7

Comparison of Area Under the Curve by Trapezoidal Rule and Fitted Equation

SUBJECT	FLUID	AUC* TRAPEZOIDAL RULE NG.HR/ML	AUC** CURVE FIT NG.HR/ML	DIFFERENCE TRAPEZOIDAL RULE MINUS CURVE FIT	CURVE FIT AS % TRAPEZOIDAL RULE
1	PLASMA	710.17	692.34	17.83	97.49
2	PLASMA	511.89	503.01	8.88	98.27
3	PLASMA	1058.06	1022.39	35.67	96.63
4	PLASMA	1118.29	1073.80	44.49	96.02
5	PLASMA	985.85	930.48	55.37	94.38
6	PLASMA	1144.01	1114.84	29.17	97.45
7	PLASMA	2178.82	2141.96	36.86	98.31
8	PLASMA	821.63	722.71	98.92	87.96
	MEAN	1066.09	1025.19	40.93	95.81
	SD	499.58	498.79	27.61	3.43
	CV(%)	46.86	48.65	67.44	3.58
	MAX	2178.82	2141.96	98.92	98.31
	MIN	511.89	503.01	8.88	87.96
1	BLOOD	625.06	603.70	21.36	96.58
2	BLOOD	394.21	372.14	22.07	94.40

* Calculated using the linear trapezoidal rule for the measured concentrations and adding the area extrapolated to zero drug concentration (obtained by dividing the last measured concentration by the elimination rate constant K10 from the curve fitting).

** The area from time zero to infinity for the equation fit to the observed data. This is the integral of the equation:
$C(T') = [D*K01/(V/F)/(K01-K10)]*[EXP(-K10*T')-EXP(-K01*T']$
where $T' = T-TLAG$

Table 8

Elimination Rate Constant and Plasma Halflife of WR6026
Calculated from the Urinary Excretion of WR6026

Subject	Elimination Rate /hr	Halflife hrs
1	.050	13.9
2	.112	6.2
3	.042	16.5
4	.042	16.5
5	.048	14.4
6	.043	16.1
7	.065	10.7
8	.079	8.9
MEAN	.060	11.6[1]
STD. DEV.	.025	

[1] Geometric Mean

Table 9

Pharmacokinetic Data for Individual Subjects

SUBJ	DATA SOURCE	WEIGHT	VOLUME/F L	KO1 /HR	K10 /HR	TLAG HR	F*KURINE	CALCULATED AMT in URINE ug	RECOVERED AMT in URINE ug	CALCULATED Plasma AUC NG.HR/ML	Trapezoidal Plasma AUC NG.HR/ML	TMAX HR	CMAX NG/ML	TIME of PEAK HR	PEAK CONC NG/ML
1	Urine				0.050		0.00028	282	279		795			3.5	57.2
1	Plasma	-2	814	1.36	0.088	0.89			279	692	710	3.0	50.3	3.5	57.2
1	PlasmatUrine	-2	1043	2.30	0.057	0.92	0.00032	271	279	831	771	2.6	43.2	3.5	57.2
1	PlasmatUrine	-1	946	1.95	0.057	0.91	0.00031	271	279	924	771	2.8	47.1	3.5	57.2
1	PlasmatUrine	0	899	1.86	0.055	0.91	0.00031	273	279	935	777	2.9	49.4	3.5	57.2
2	Urine				0.112		0.00044	199	197		554			1.5	75.4
2	Plasma	-2	512	1.32	0.192	0.44			197	503	512	2.2	69.6	1.5	75.4
2	PlasmatUrine	-2	686	2.16	0.132	0.45	0.00051	190	197	545	539	1.8	60.2	1.5	75.4
2	PlasmatUrine	-1	604	1.83	0.141	0.45	0.00054	189	197	581	533	2.0	66.2	1.5	75.4
2	PlasmatUrine	0	590	1.84	0.135	0.46	0.00053	191	197	622	537	2.0	68.2	1.5	75.4
3	Urine				0.042		0.00045	536	537		1094			3.0	52.5
3	Plasma	-2	1014	0.72	0.048	0.79			537	1022	1058	4.8	40.3	3.0	52.5
3	PlasmatUrine	-2	1106	1.04	0.046	0.85	0.00050	522	537	963	1069	4.0	38.7	3.0	52.5
3	PlasmatUrine	-1	1041	1.07	0.046	0.89	0.00049	523	537	1042	1069	4.0	41.3	3.0	52.5
3	PlasmatUrine	0	1008	1.21	0.045	0.95	0.00049	525	537	1101	1075	3.8	43.3	3.0	52.5
4	Urine				0.042		0.00026	267	300		1196			2.5	85.6
4	Plasma	-2	693	1.15	0.067	0.36			300	1074	1118	3.0	59.9	2.5	85.6
4	PlasmatUrine	-2	759	1.24	0.056	0.35	0.00033	289	300	1160	1144	3.0	56.3	2.5	85.6
4	PlasmatUrine	-1	683	1.41	0.058	0.41	0.00034	288	300	1252	1137	2.8	63.3	2.5	85.6
4	PlasmatUrine	0	632	1.54	0.059	0.46	0.00035	287	300	1317	1136	2.7	68.7	2.5	85.6
5	Urine				0.048		0.00018	208	181		1045			5.0	72.0
5	Plasma	-2	699	0.44	0.076	0.88			181	931	986	5.7	49.2	5.0	72.0
5	PlasmatUrine	-2	984	0.19	0.047	0.00	0.00017	179	181	1070	1048	9.8	31.7	5.0	72.0
5	PlasmatUrine	-1	867	0.61	0.041	0.95	0.00015	180	181	1382	1072	5.7	46.9	5.0	72.0
5	PlasmatUrine	0	748	0.69	0.046	1.11	0.00017	179	181	1435	1052	5.3	54.6	5.0	72.0
6	Urine				0.043		0.00040	477	456		1172			3.0	62.3
6	Plasma	-2	876	0.83	0.051	0.32			456	1115	1144	3.9	47.1	3.0	62.3
6	PlasmatUrine	-2	946	0.43	0.040	0.04	0.00039	447	456	1299	1186	6.1	41.0	3.0	62.3
6	PlasmatUrine	-1	919	0.88	0.038	0.35	0.00037	449	456	1428	1196	4.1	46.8	3.0	62.3
6	PlasmatUrine	0	862	0.99	0.039	0.43	0.00038	447	456	1480	1191	3.8	50.3	3.0	62.3
7	Urine				0.065		0.00207	1871	1565		2147			2.0	116.0
7	Plasma	-2	416	0.63	0.055	0.42			1565	2142	2179	4.6	94.1	2.0	116.0
7	PlasmatUrine	-2	382	0.50	0.060	0.40	0.00191	1551	1565	2169	2162	5.2	97.3	2.0	116.0
7	PlasmatUrine	-1	403	0.78	0.056	0.46	0.00180	1559	1565	2136	2175	4.1	100.2	2.0	116.0
7	PlasmatUrine	0	429	1.76	0.054	0.70	0.00175	1563	1565	2135	2183	2.8	103.4	2.0	116.0
8	Urine				0.078		0.00067	547	503		825			3.8	66.9
8	Plasma	-2	844	0.58	0.081	0.30			503	723	822	4.3	42.6	3.8	66.9
8	PlasmatUrine	-2	810	0.41	0.080	0.19	0.00082	503	503	760	823	5.1	41.1	3.8	66.9
8	PlasmatUrine	-1	754	0.68	0.075	0.41	0.00077	505	503	877	828	4.1	49.9	3.8	66.9
8	PlasmatUrine	0	706	1.17	0.074	0.70	0.00076	504	503	947	829	3.2	58.2	3.8	66.9

Table 10

Pharmacokinetic Parameters for Individual Subjects
Estimated Using Observed Plasma and Urinary Data[1]

SUBJ	VOLUME/F[2] L	K01[3] /HR	K10[4] /HR	TLAG[5] HR	F*KURINE[6] /HR	TMAX[7] HR	CMAX[8] NG/ML
1	1043	2.30	0.057	0.92	0.00032	2.6	43.2
2	686	2.16	0.132	0.45	0.00051	1.8	60.2
3	1106	1.04	0.046	0.85	0.00050	4.0	38.7
4	759	1.24	0.056	0.35	0.00033	3.0	56.3
5	984	0.19	0.047	0.00	0.00017	9.8	31.7
6	946	0.43	0.040	0.04	0.00039	6.1	41.0
7	382	0.50	0.060	0.40	0.00191	5.2	97.3
8	810	0.41	0.080	0.19	0.00082	5.1	41.1
MEAN	840	1.03	0.065	0.40	0.00062	4.7	51.2
SD	234	0.82	0.030	0.34	0.00056	2.5	20.8
CV(%)	28	78.97	45.939	85.13	89.77831	53.9	40.7
MAX	1106	2.30	0.132	0.92	0.00191	9.8	97.3
MIN	382	0.19	0.040	0.00	0.00017	1.8	31.7

1 Observed data weighted to the reciprocal of the square of the number
2 Volume of distribution divided by fraction available, F
3 Absorption rate constant
4 Elimination rate constant
5 Time delay before onset of absorption
5 Area under the concentration time curve for the equation fit to the plasma concentrations
6 Rate constant of elimination of unchanged drug into the urine times the fraction available
7 Time at which maximum concentration occurs according to fitted equation
8 Maximum concentration from fitted equation

Figure 1

Chemical Structure of WR 6026

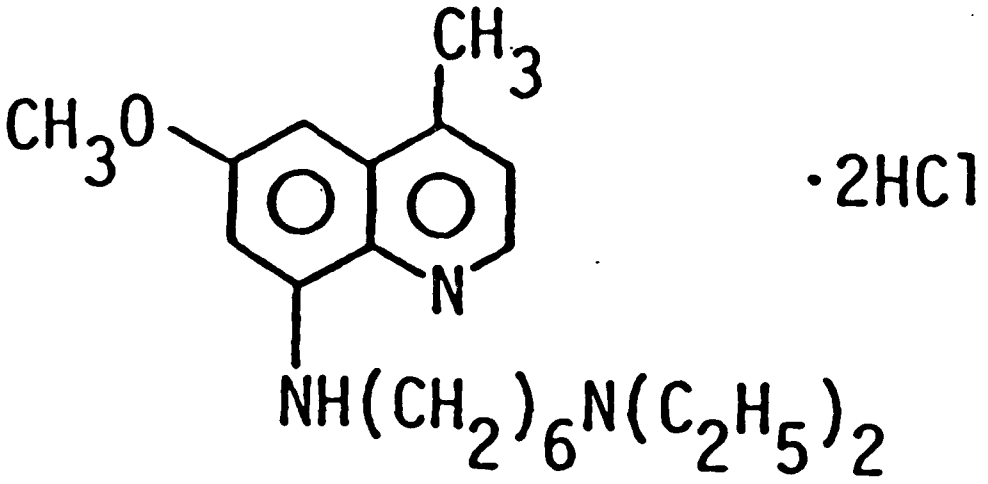


Figure 2

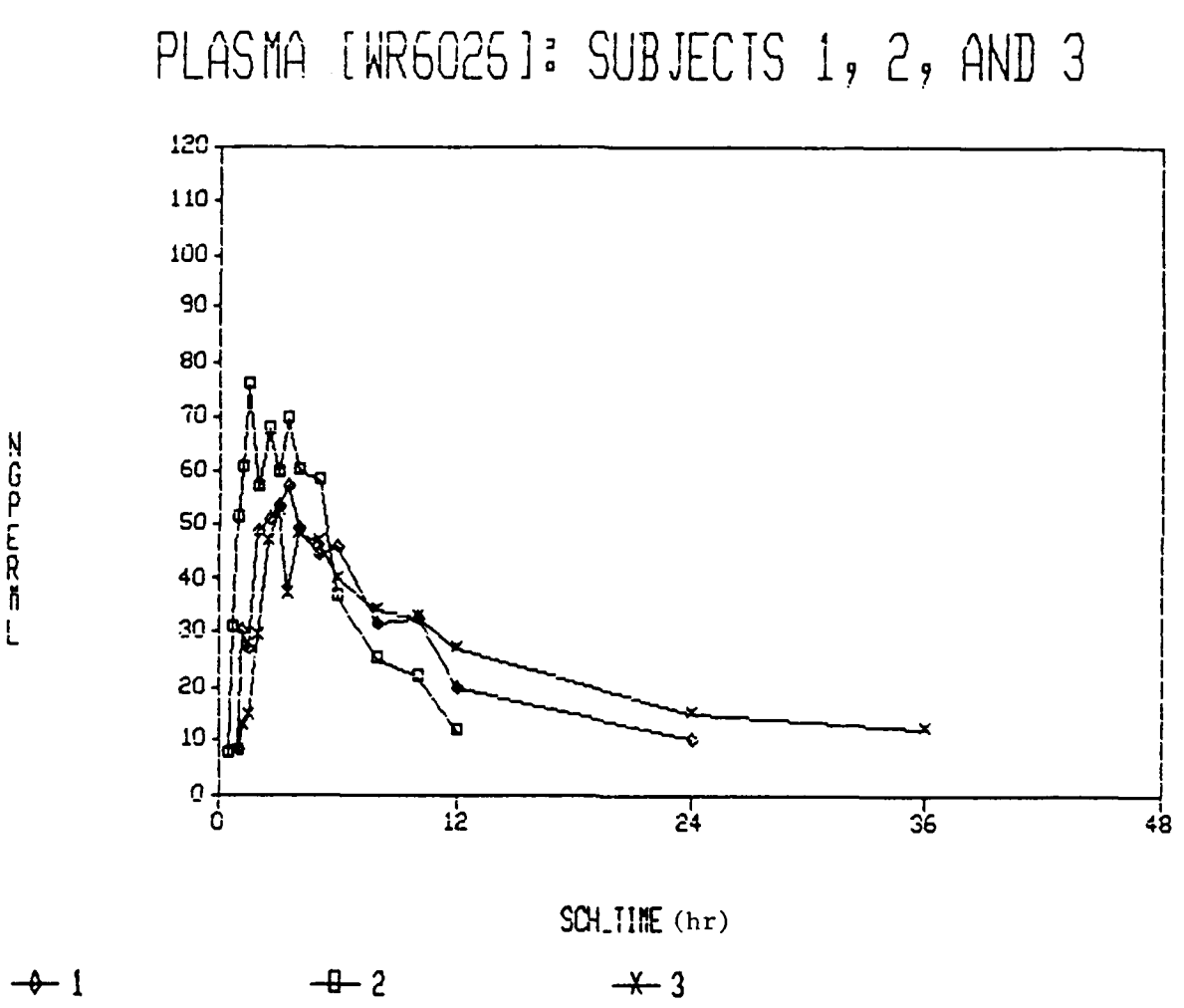

PLASMA [WR6025]: SUBJECTS 1, 2, AND 3
NGPLERE
120
110
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
SCH_TIME (hr)
1
2
3

Figure 3

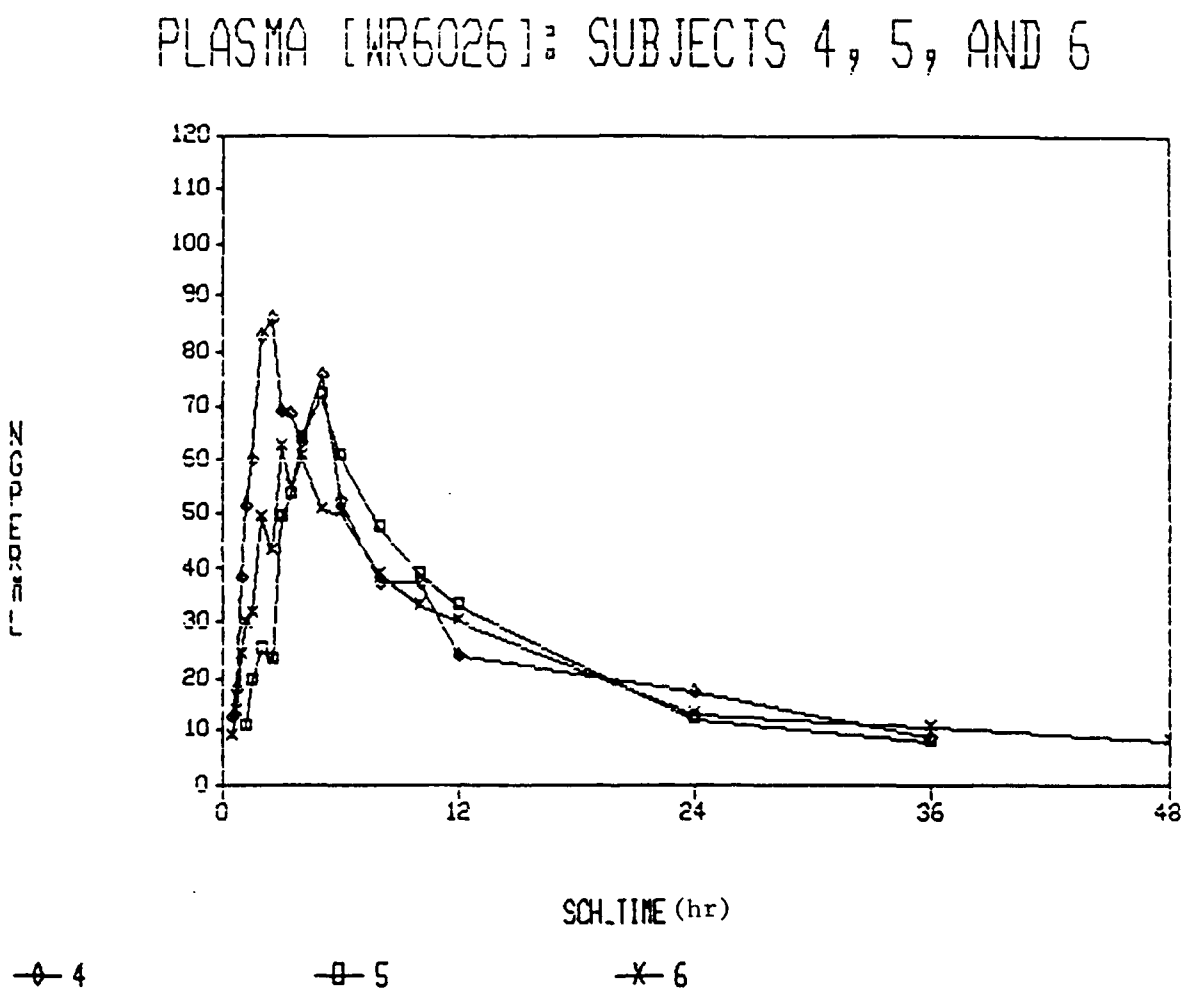

PLASMA [WR60261: SUBJECTS 4, 5, AND 6
120
110
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
SCH_TIME (hr)
4
5
6

Figure 4

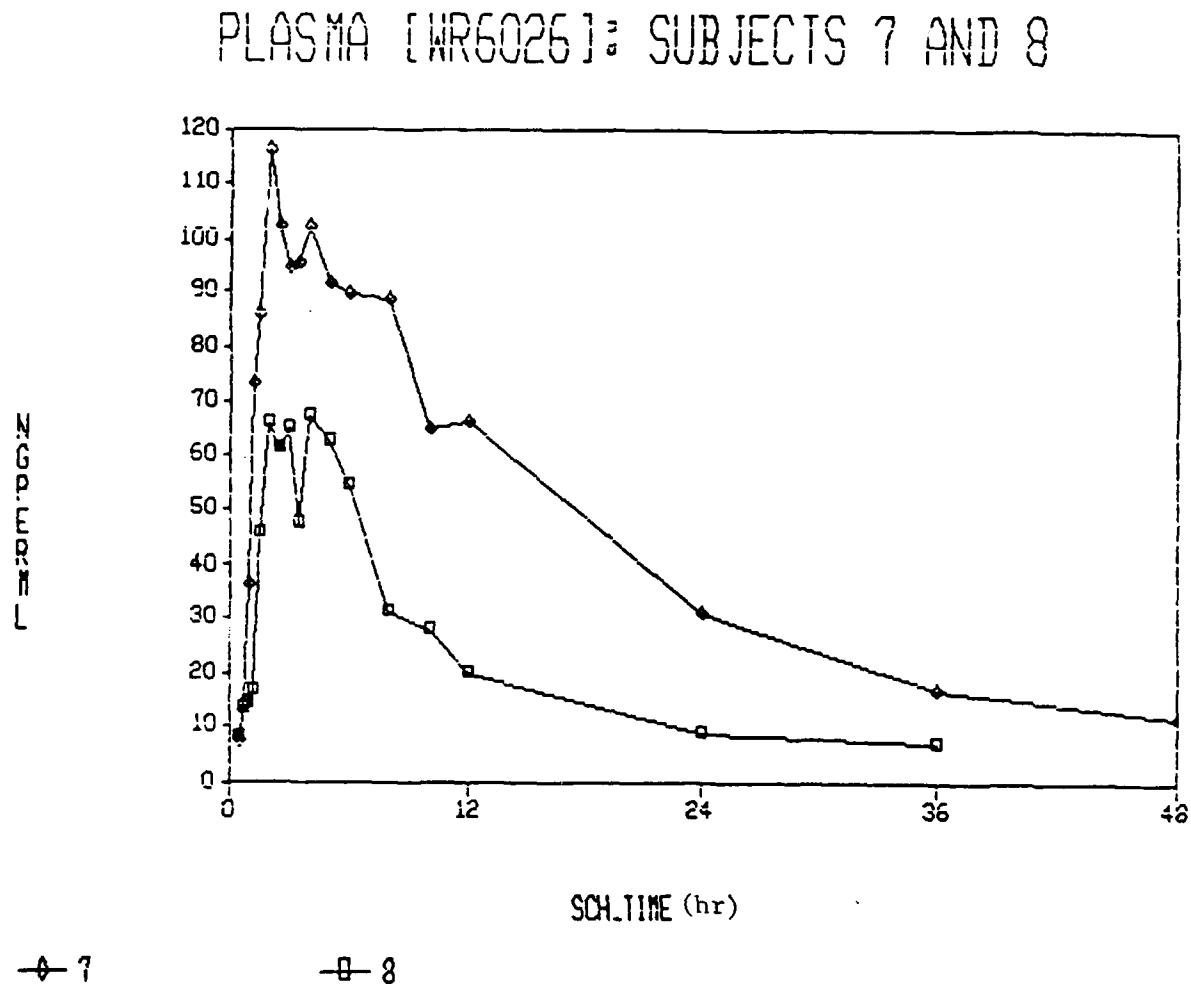

PLASMA [WR6026]: SUBJECTS 7 AND 8
NGPERML
120
110
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
SCH_TIME (hr)
7
8

Figure 5

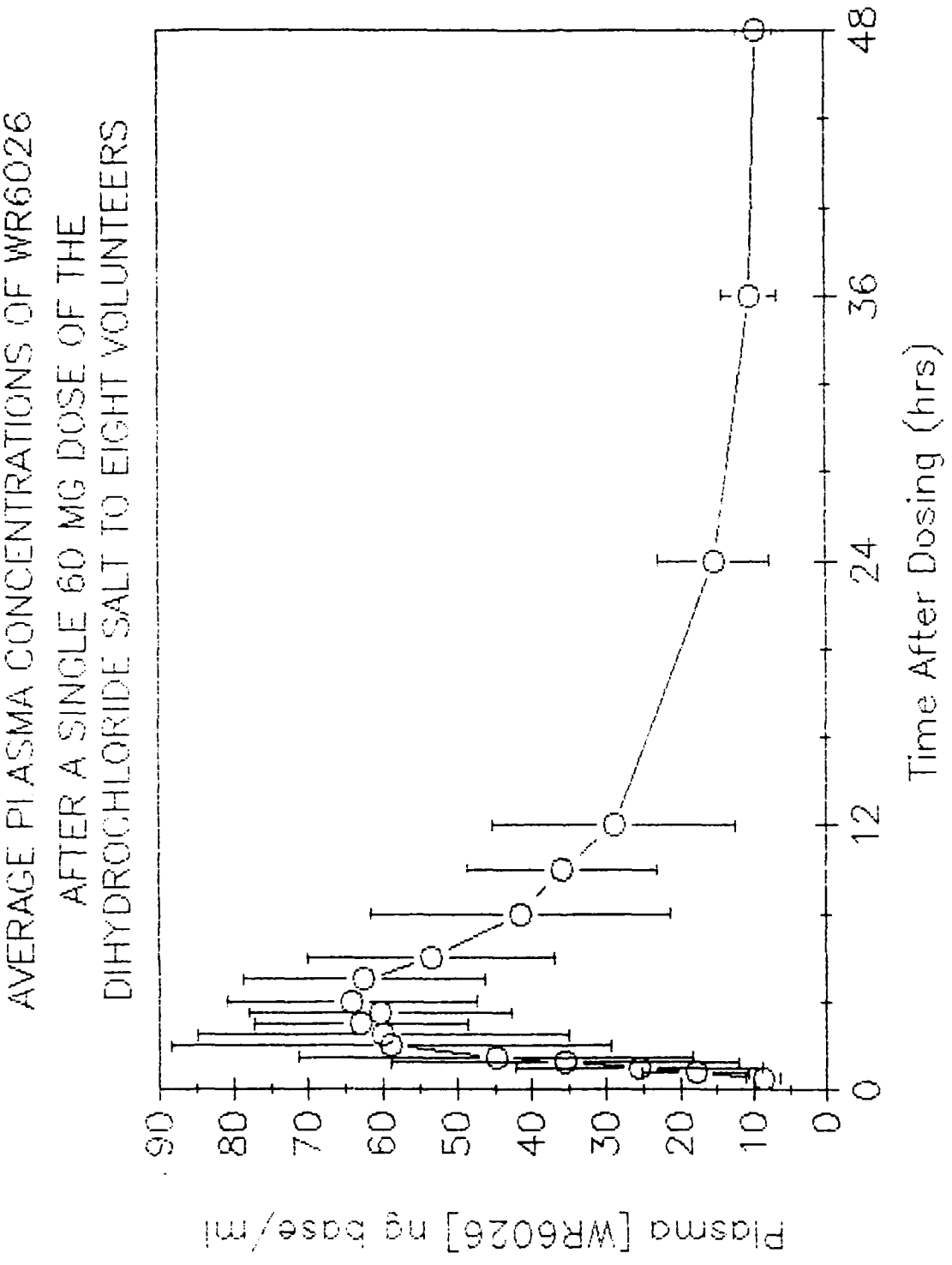

AVERAGE PLASMA CONCENTRATIONS OF WR6026
AFTER A SINGLE 60 MG DOSE OF THE
DIHYDROCHLORIDE SALT TO EIGHT VOLUNTEERS
Plasma [WR6026] ng base/ml
0
10
20
30
40
50
60
70
80
90
0
12
24
36
48
Time After Dosing (hrs)

Figure 6

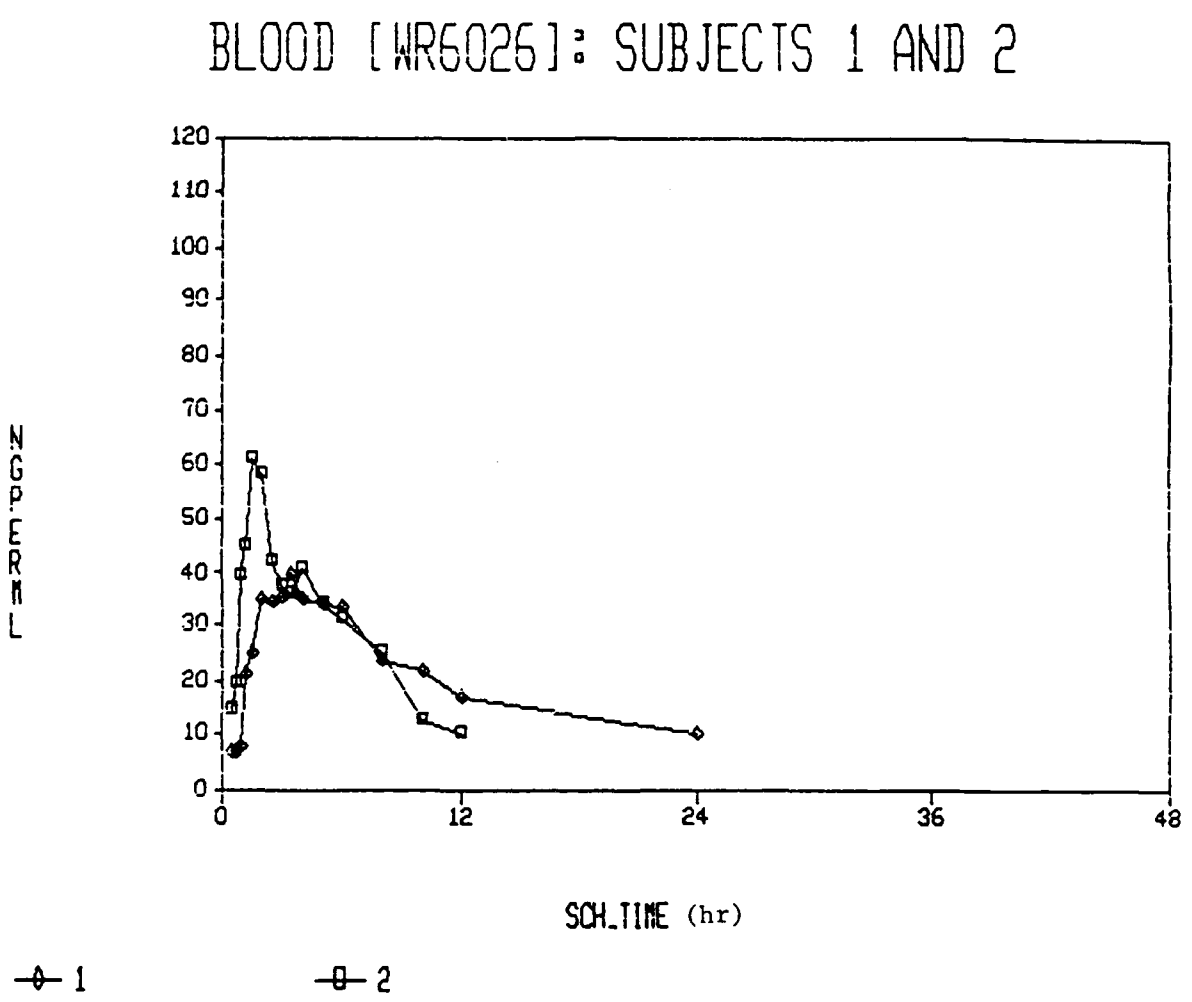

BLOOD [WR6026]: SUBJECTS 1 AND 2
NG/ML
120
110
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
SCH_TIME (hr)
1
2

Figure 7

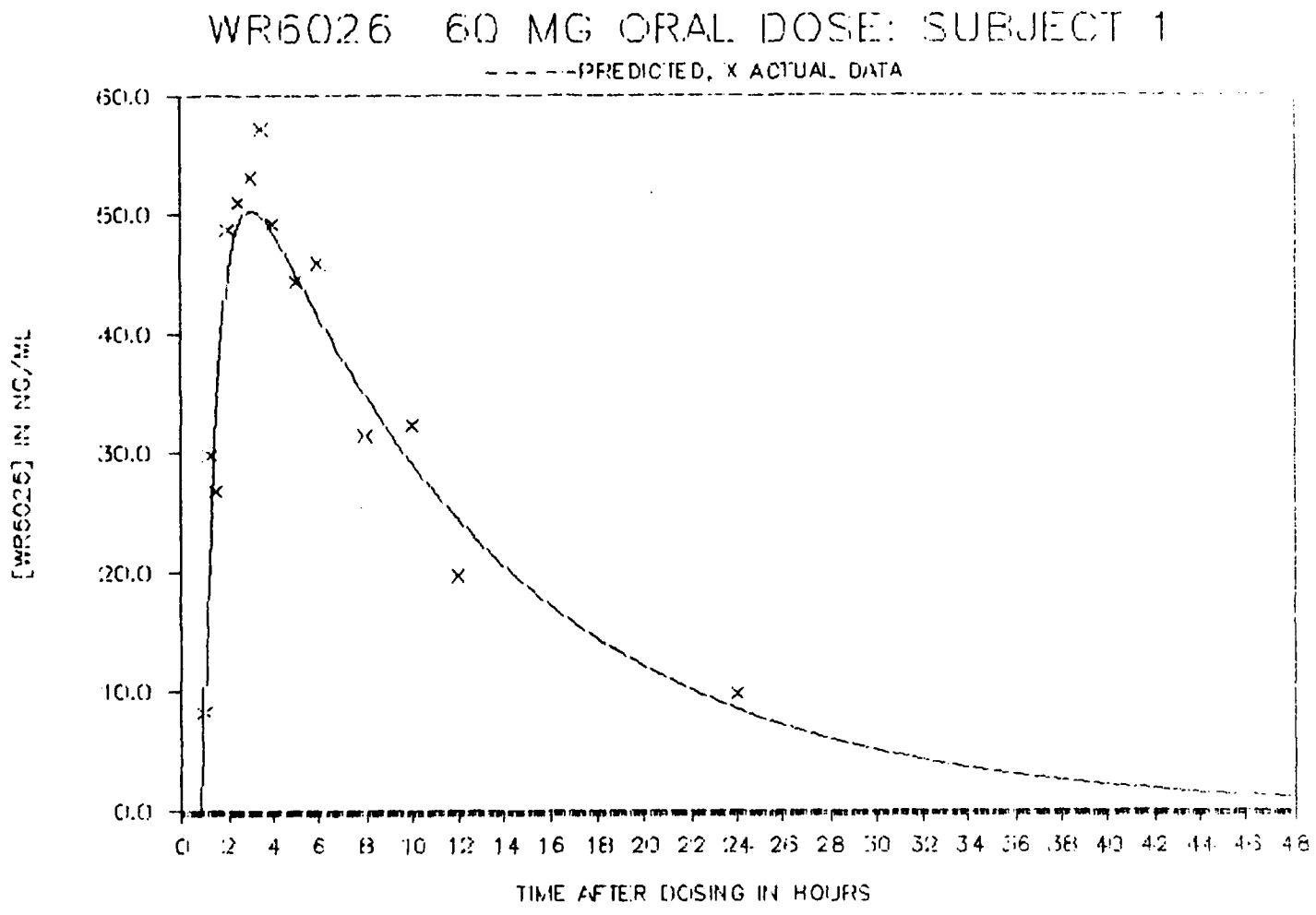

WR6026 60 MG ORAL DOSE: SUBJECT 1
-----PREDICTED, X ACTUAL DATA
[WR6026] IN NG/ML
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
TIME AFTER DOSING IN HOURS

Figure 8

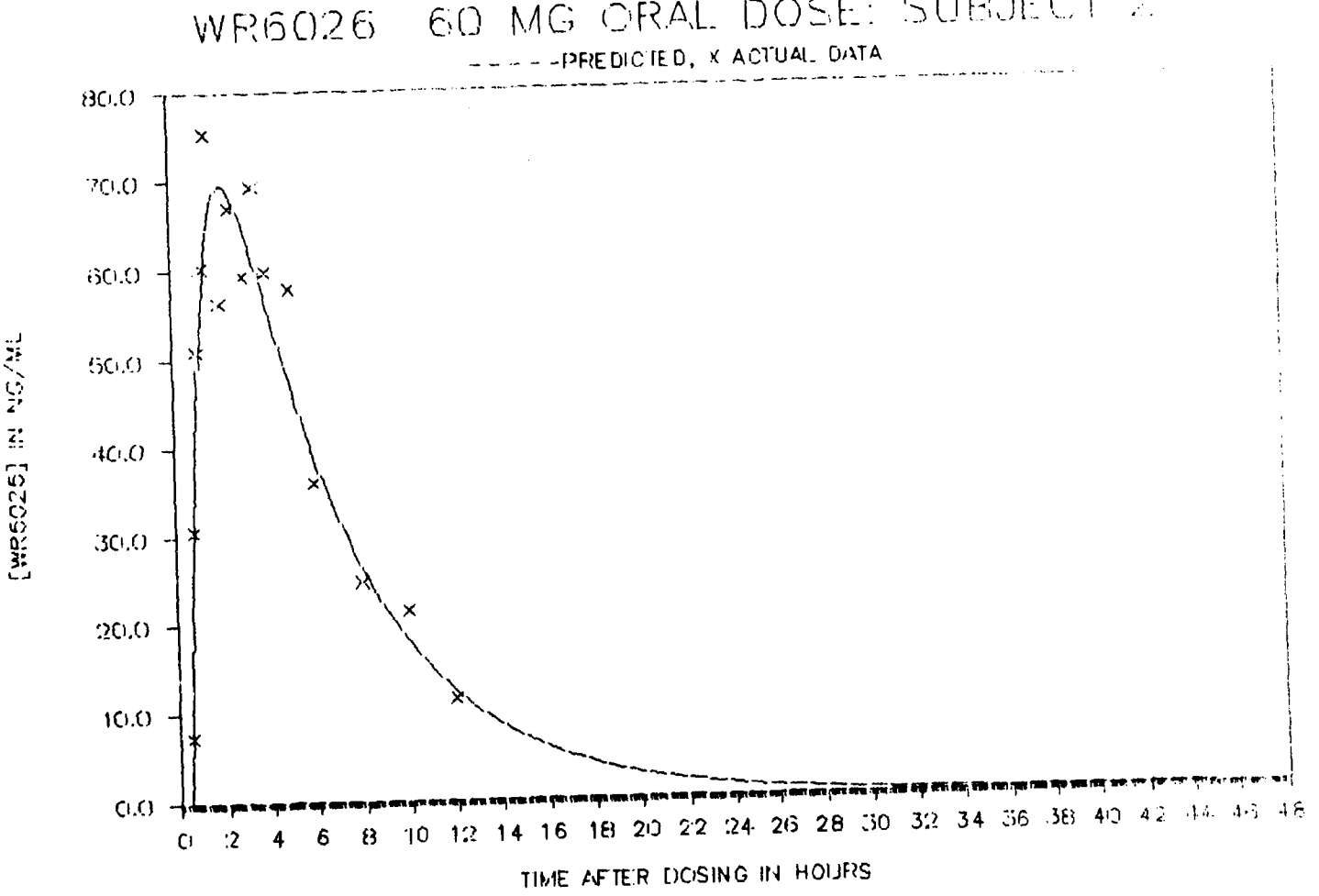

WR6026 60 MG ORAL DOSE: SUBJECT 2
-----PREDICTED, x ACTUAL DATA
[WR6026] IN NG/ML
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46
TIME AFTER DOSING IN HOURS

Figure 9

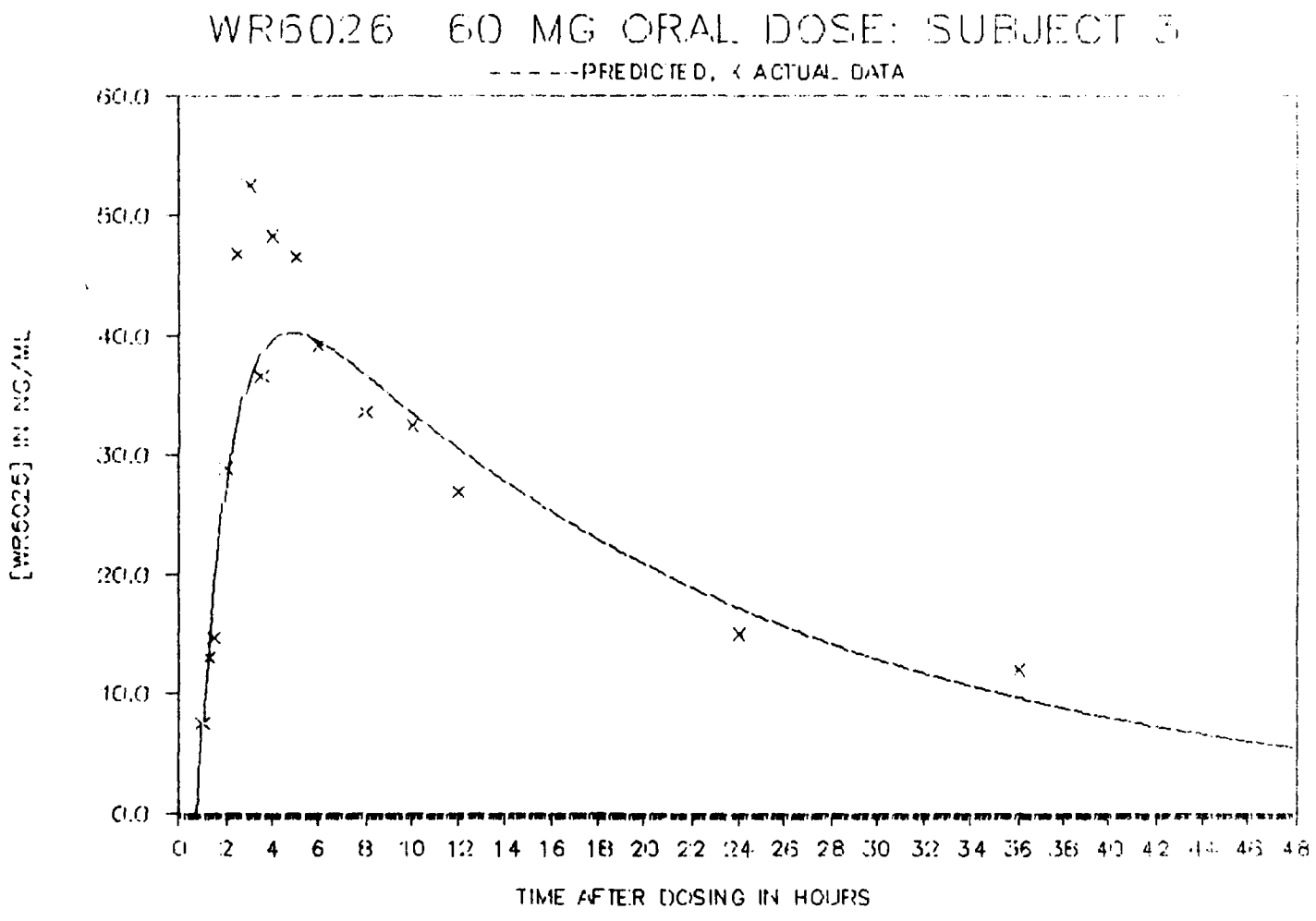

WR6026 60 MG ORAL DOSE: SUBJECT 3
-----PREDICTED, x ACTUAL DATA
[WR6026] IN NG/ML
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
TIME AFTER DOSING IN HOURS

Figure 10

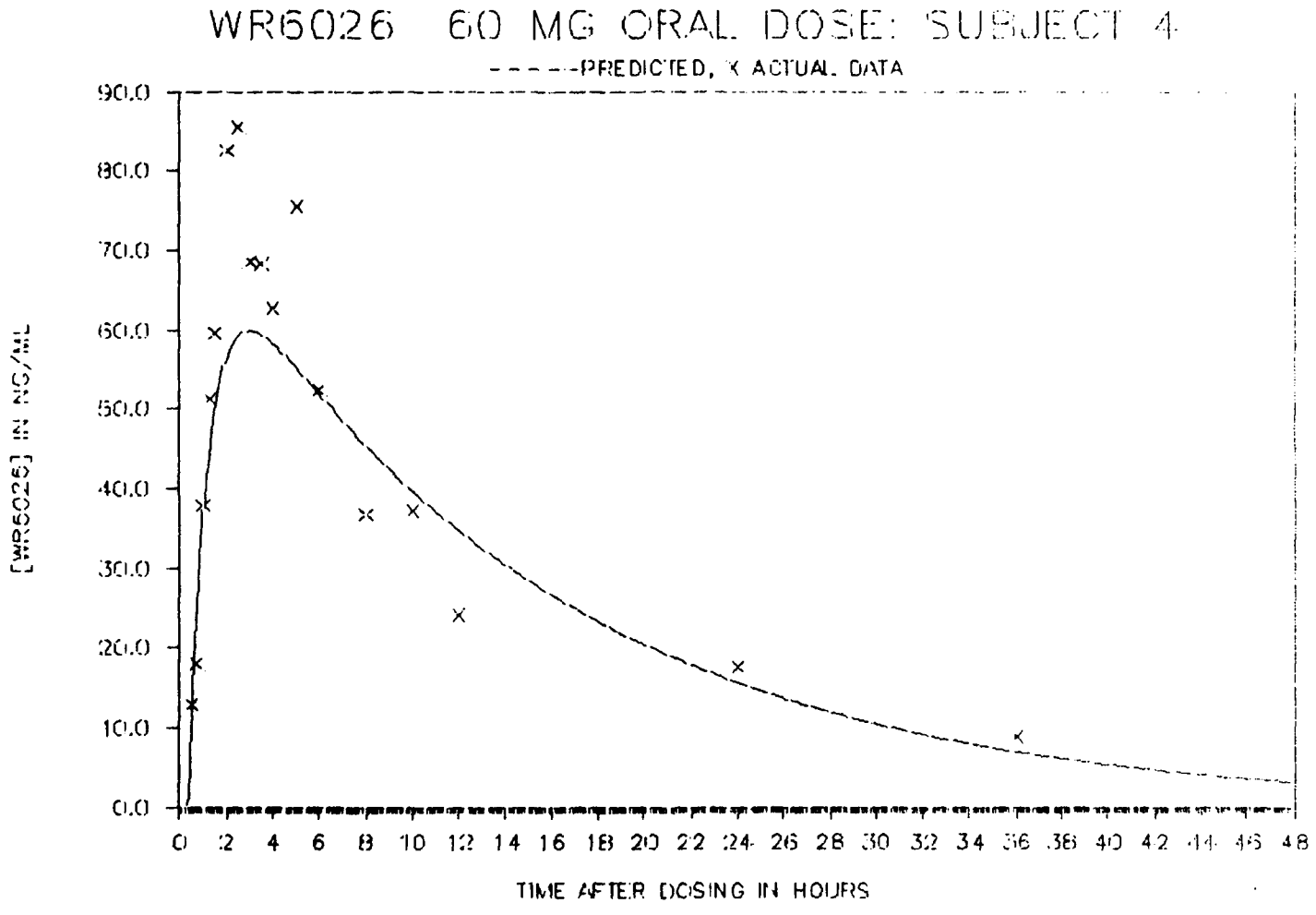

WR6026 60 MG ORAL DOSE: SUBJECT 4
-----PREDICTED, X ACTUAL DATA
[WR6026] IN NG/ML
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
TIME AFTER DOSING IN HOURS

Figure 11

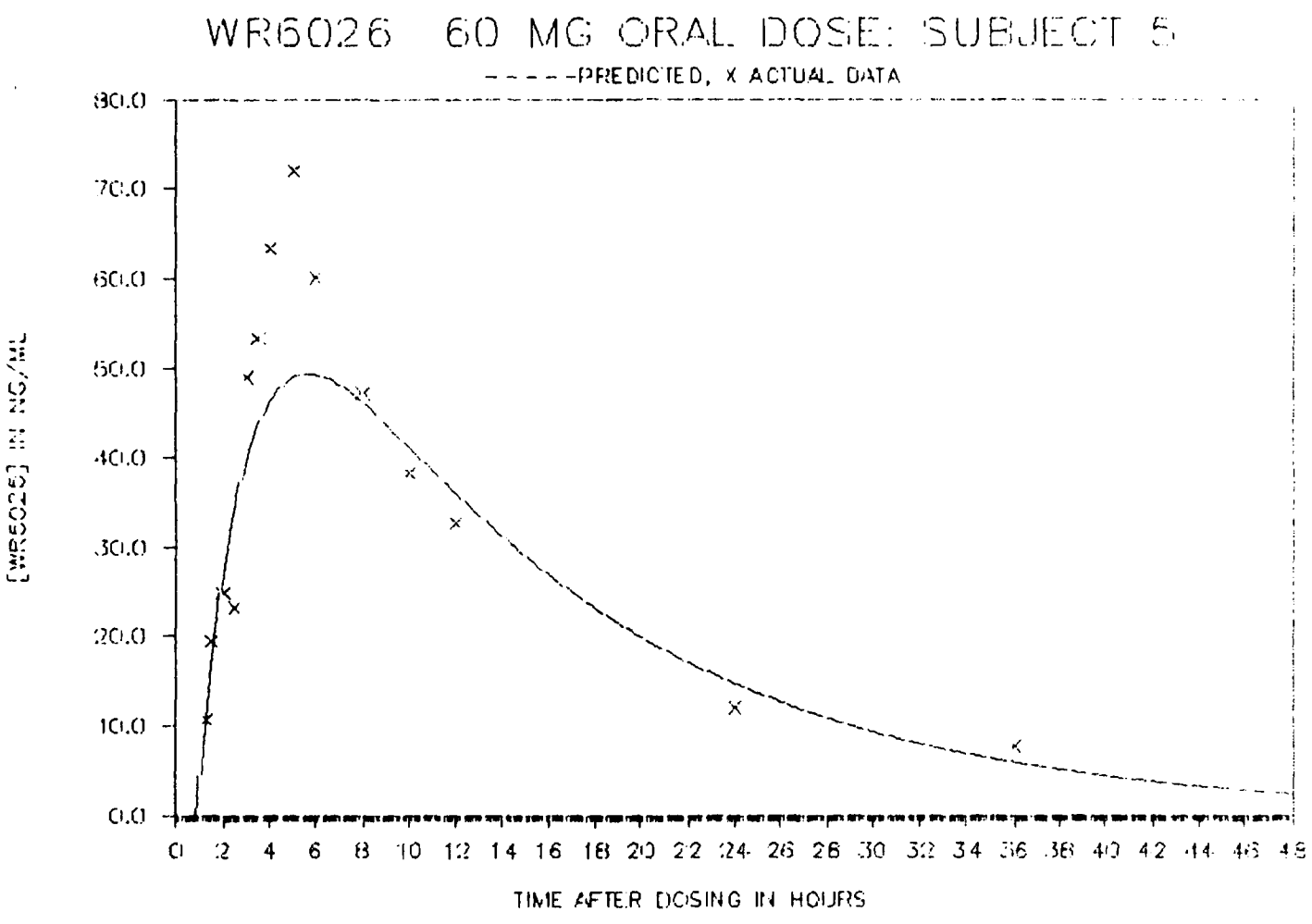

WR6026 60 MG ORAL DOSE: SUBJECT 5
-----PREDICTED, X ACTUAL DATA
[WR6026] IN NG/ML
800.0
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
TIME AFTER DOSING IN HOURS

Figure 12

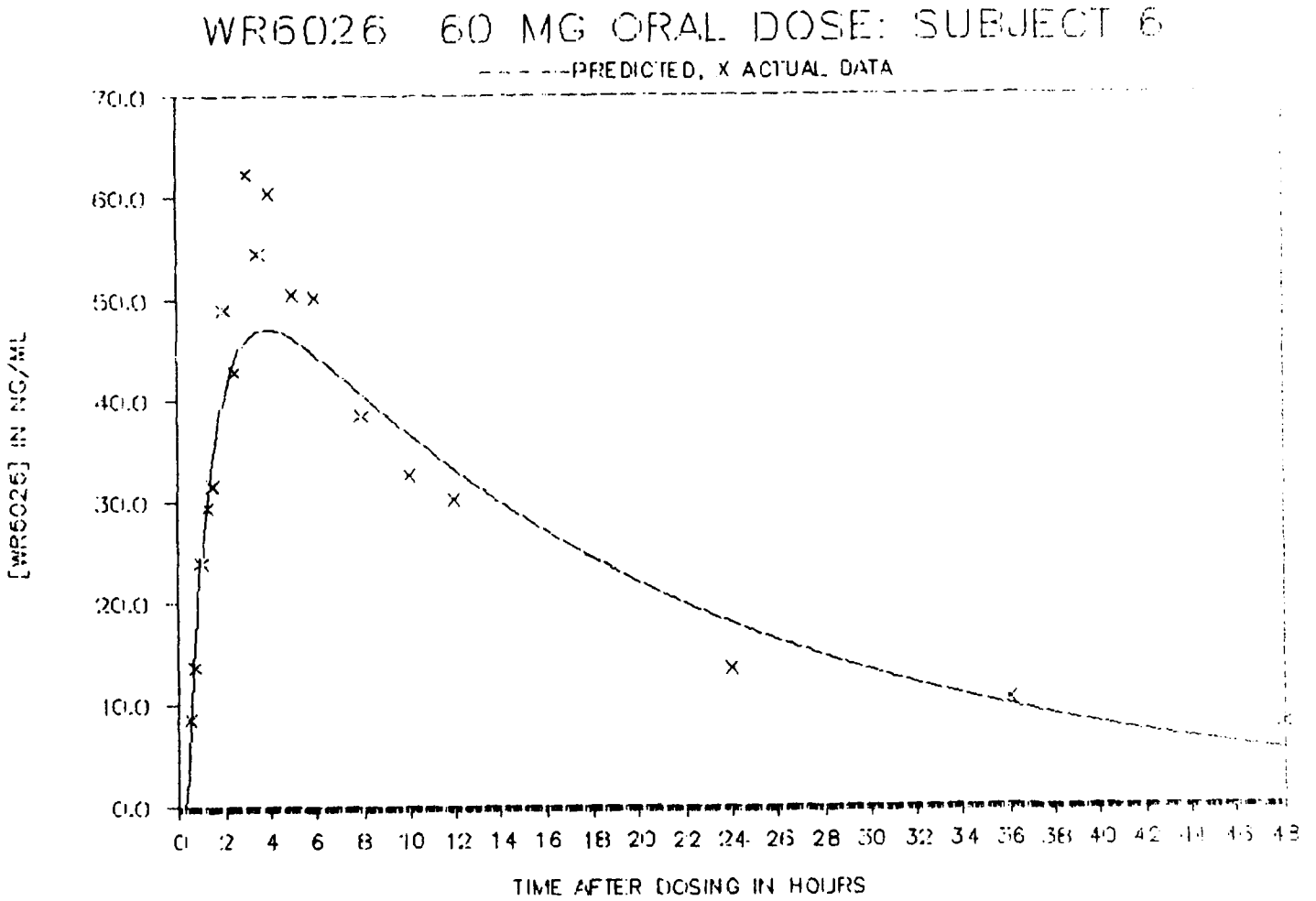

WR6026 60 MG ORAL DOSE: SUBJECT 6
----PREDICTED, X ACTUAL DATA
[WR6026] IN NG/ML
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
TIME AFTER DOSING IN HOURS

Figure 13

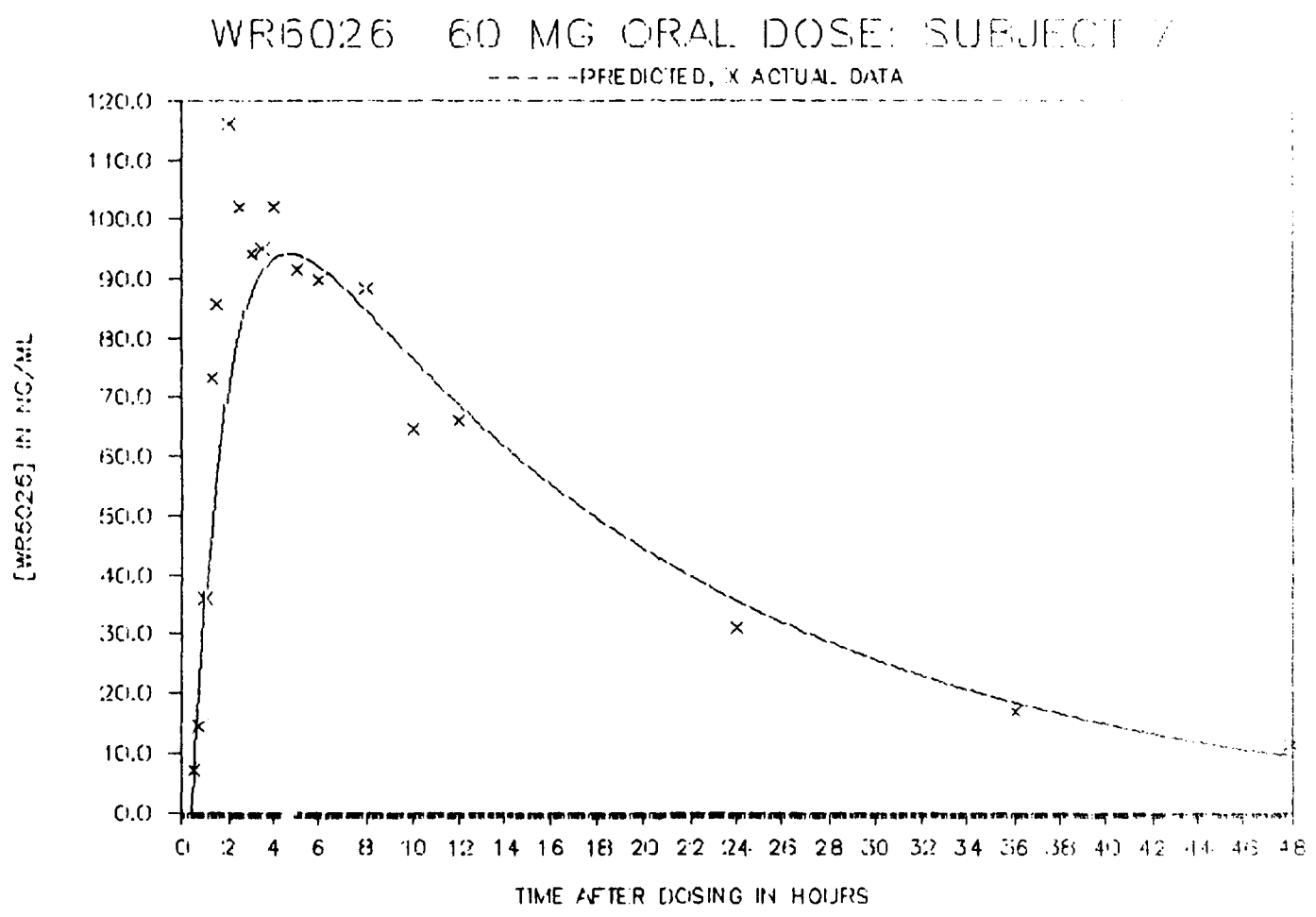

WR6026 60 MG ORAL DOSE: SUBJECT 7
-----PREDICTED, X ACTUAL DATA
[WR6026] IN NG/ML
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
TIME AFTER DOSING IN HOURS

Figure 14

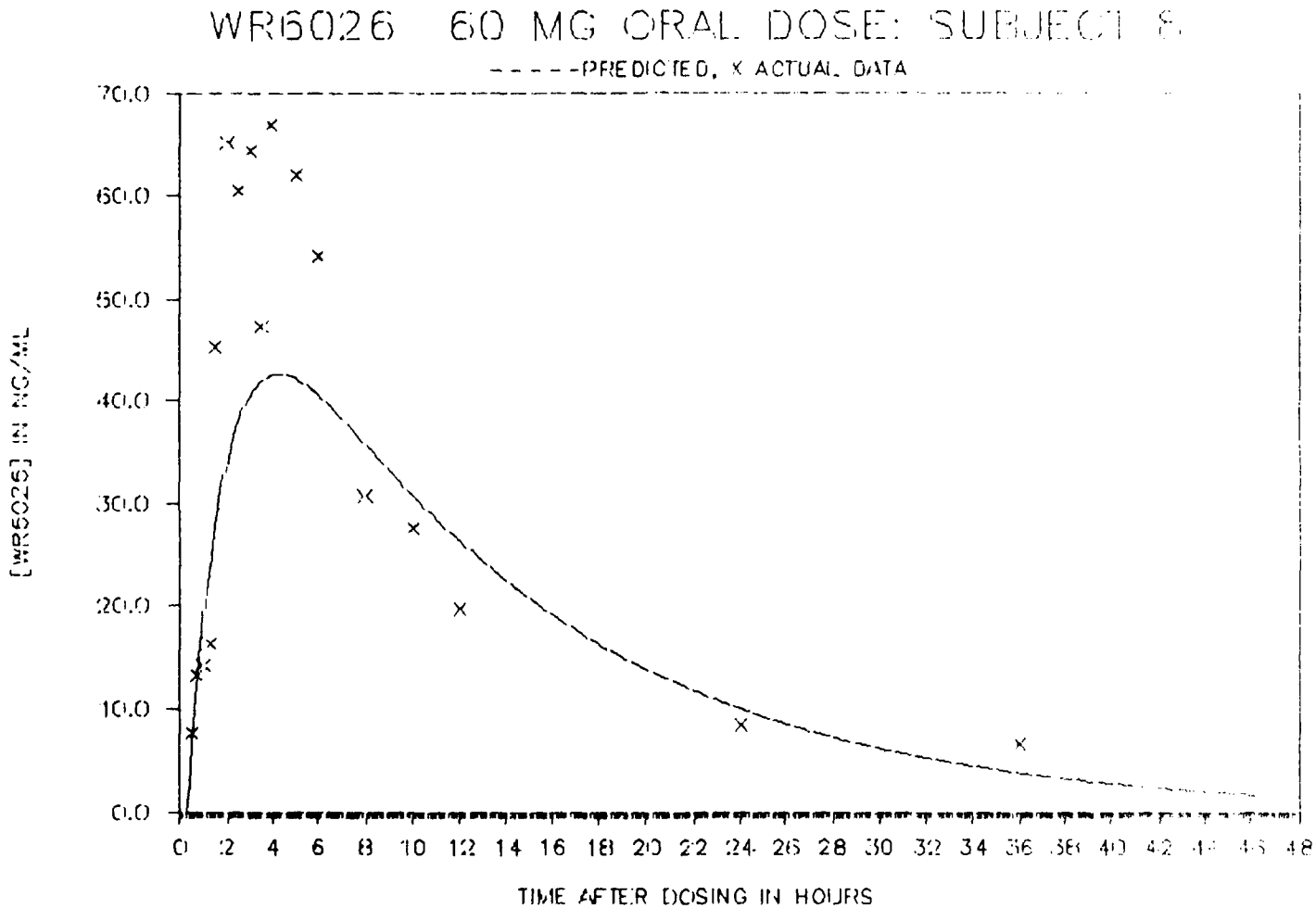

WR6026 60 MG ORAL DOSE: SUBJECT 8
-----PREDICTED, X ACTUAL DATA
[WR6026] IN NG/ML
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
TIME AFTER DOSING IN HOURS

Figure 15

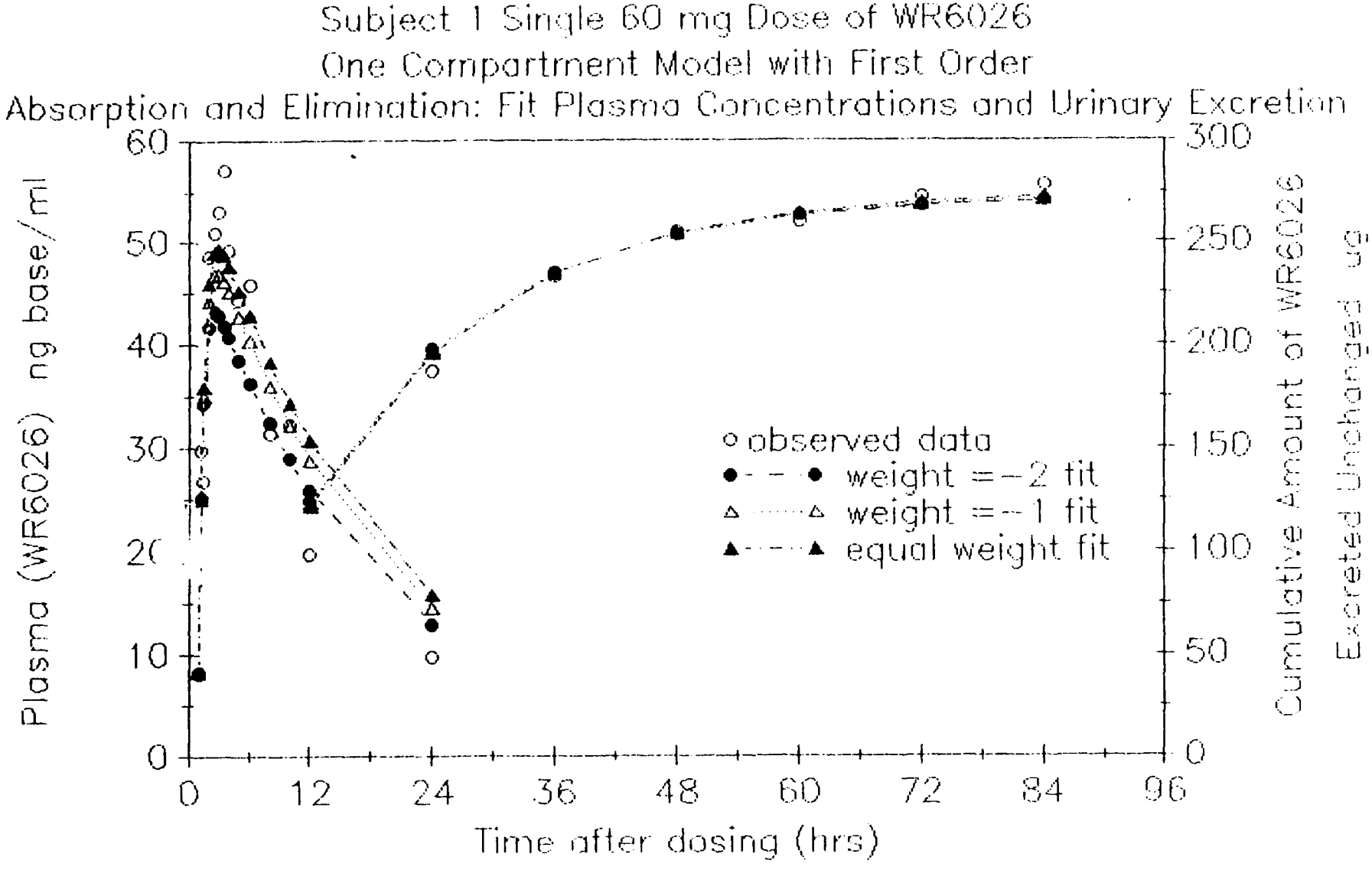

Subject 1 Single 60 mg Dose of WR6026
One Compartment Model with First Order
Absorption and Elimination: Fit Plasma Concentrations and Urinary Excretion
Plasma (WR6026) ng base/ml
Cumulative Amount of WR6026 Excreted Unchanged ug
Time after dosing (hrs)
observed data
weight = -2 fit
weight = -1 fit
equal weight fit
0
10
20
30
40
50
60
0
50
100
150
200
250
300
0
12
24
36
48
60
72
84
96

Figure 16

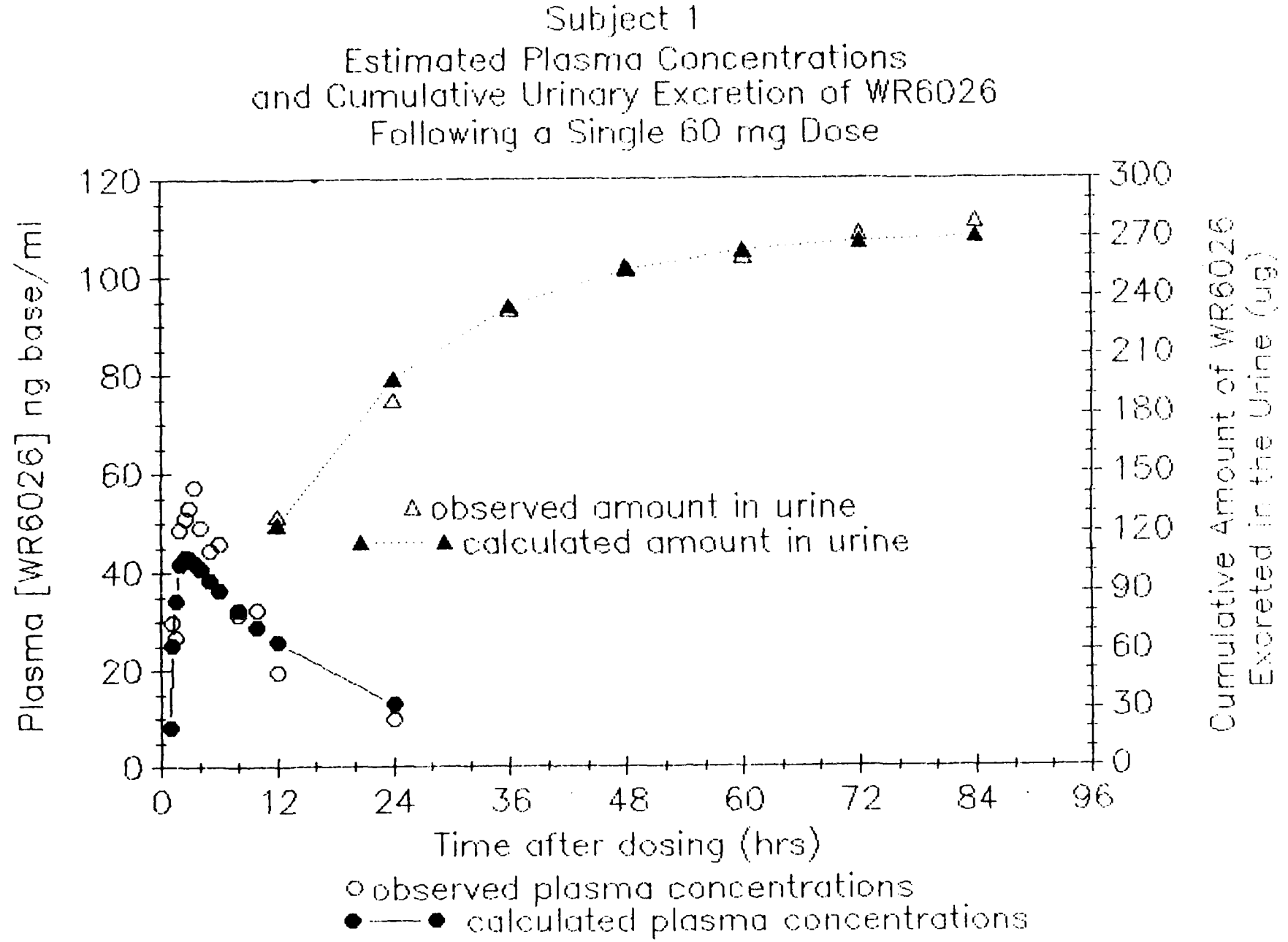

Subject 1
Estimated Plasma Concentrations
and Cumulative Urinary Excretion of WR6026
Following a Single 60 mg Dose
Plasma [WR6026] ng base/ml
Cumulative Amount of WR6026 Excreted in the Urine (ug)
Time after dosing (hrs)
observed amount in urine
calculated amount in urine
observed plasma concentrations
calculated plasma concentrations
0
20
40
60
80
100
120
0
30
60
90
120
150
180
210
240
270
300
0
12
24
36
48
60
72
84
96

Figure 17

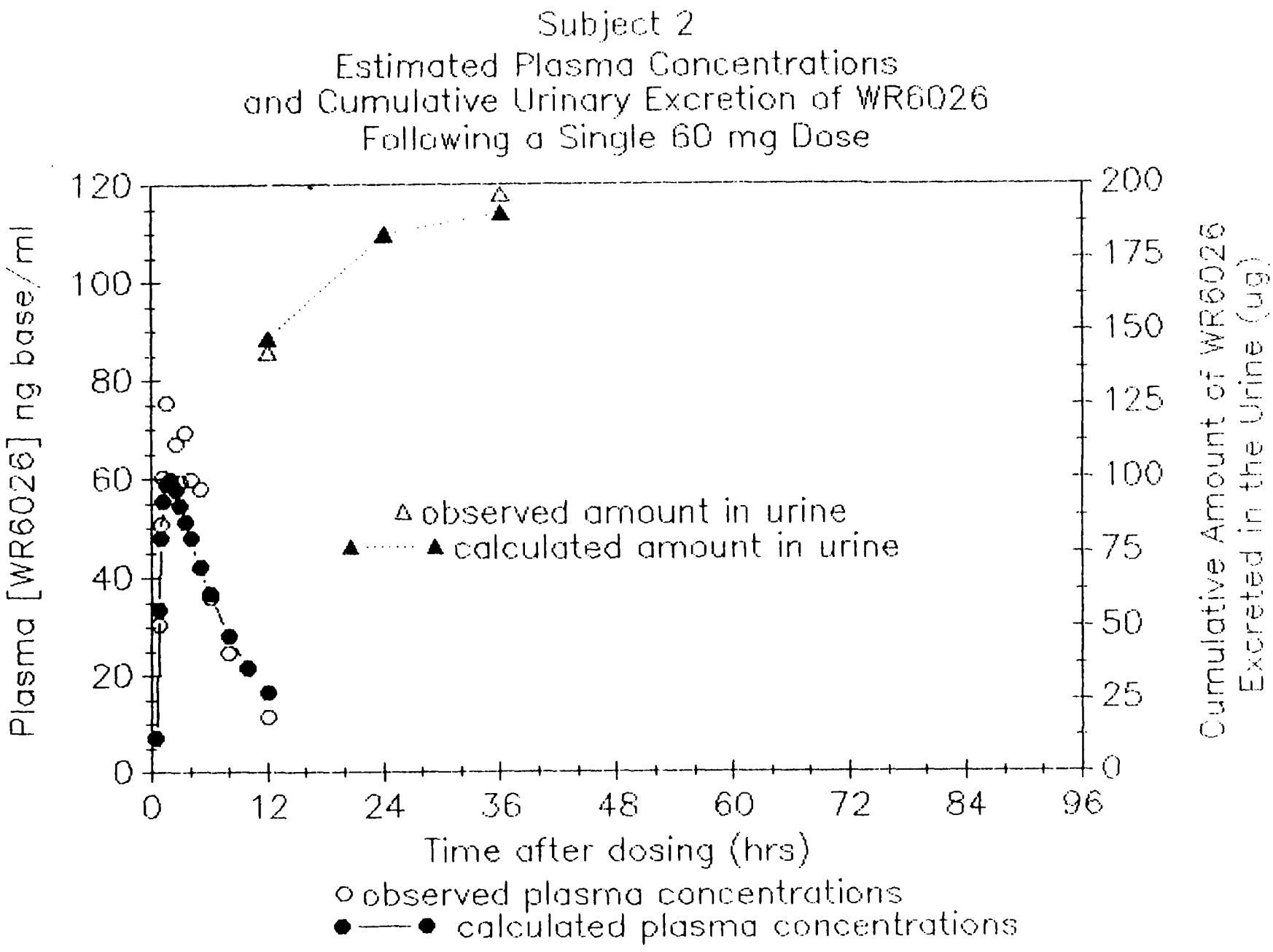

Subject 2
Estimated Plasma Concentrations
and Cumulative Urinary Excretion of WR6026
Following a Single 60 mg Dose
Plasma [WR6026] ng base/ml
Cumulative Amount of WR6026
Excreted in the Urine (ug)
Time after dosing (hrs)
0
12
24
36
48
60
72
84
96
120
100
80
60
40
20
0
200
175
150
125
100
75
50
25
0
observed amount in urine
calculated amount in urine
observed plasma concentrations
calculated plasma concentrations

Figure 18

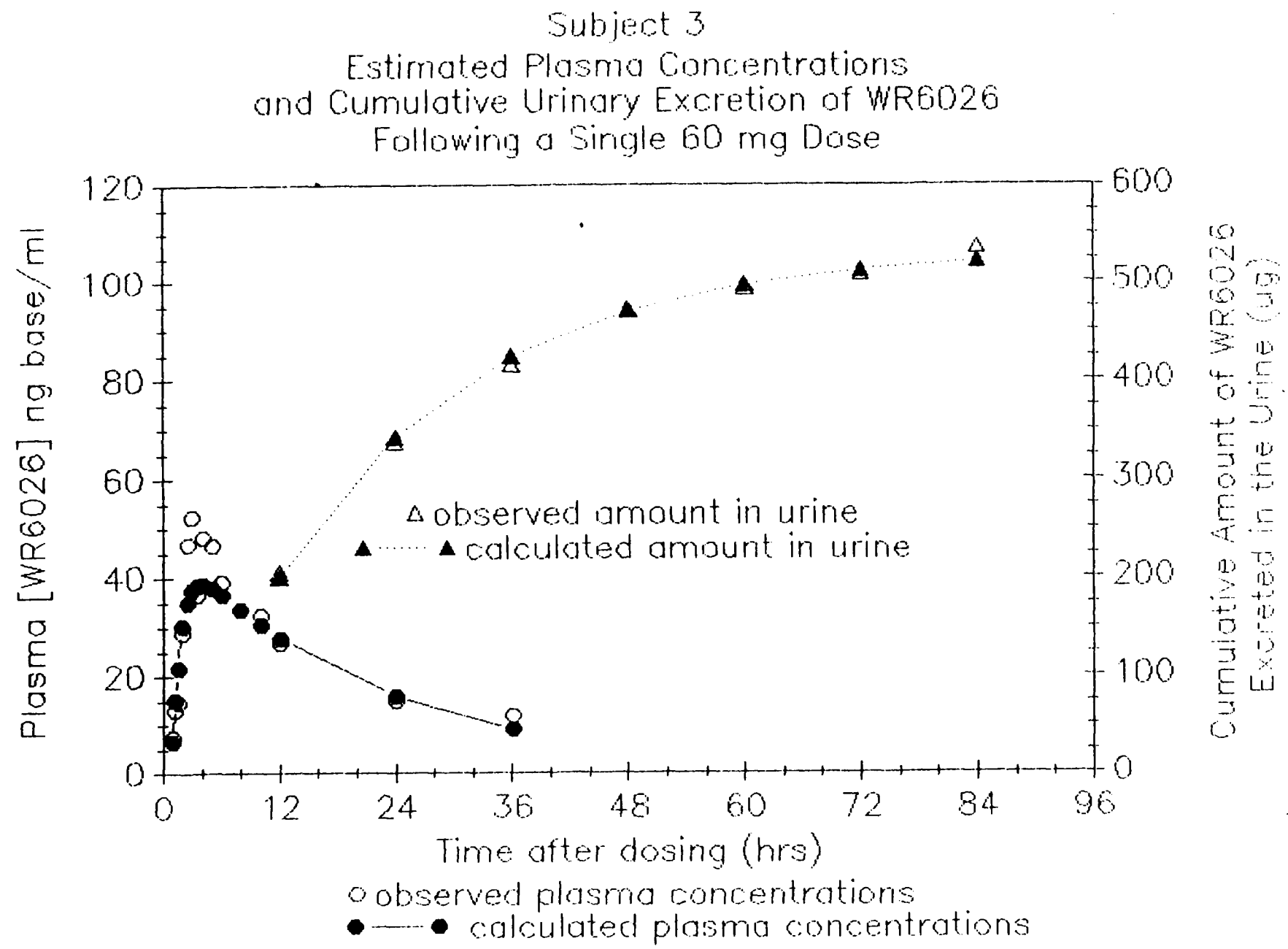

Subject 3
Estimated Plasma Concentrations
and Cumulative Urinary Excretion of WR6026
Following a Single 60 mg Dose
Plasma [WR6026] ng base/ml
Cumulative Amount of WR6026 Excreted in the Urine (µg)
Time after dosing (hrs)
△ observed amount in urine
▲ calculated amount in urine
○ observed plasma concentrations
● — ● calculated plasma concentrations
0
20
40
60
80
100
120
0
100
200
300
400
500
600
0
12
24
36
48
60
72
84
96

Figure 19

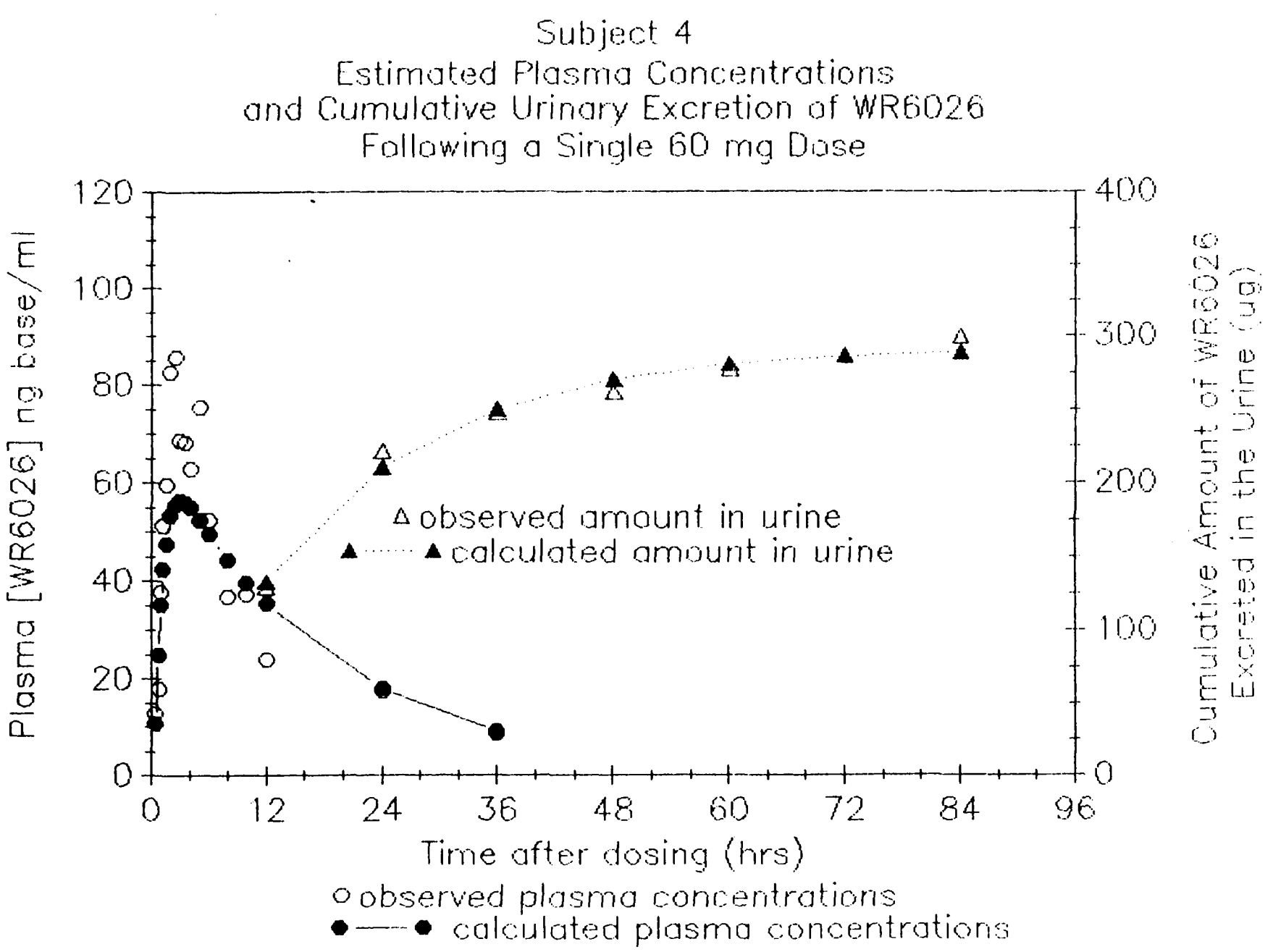

Subject 4
Estimated Plasma Concentrations
and Cumulative Urinary Excretion of WR6026
Following a Single 60 mg Dose
Plasma [WR6026] ng base/ml
Cumulative Amount of WR6026
Excreted in the Urine (ug)
Time after dosing (hrs)
0
12
24
36
48
60
72
84
96
0
20
40
60
80
100
120
0
100
200
300
400
observed amount in urine
calculated amount in urine
observed plasma concentrations
calculated plasma concentrations

Figure 20

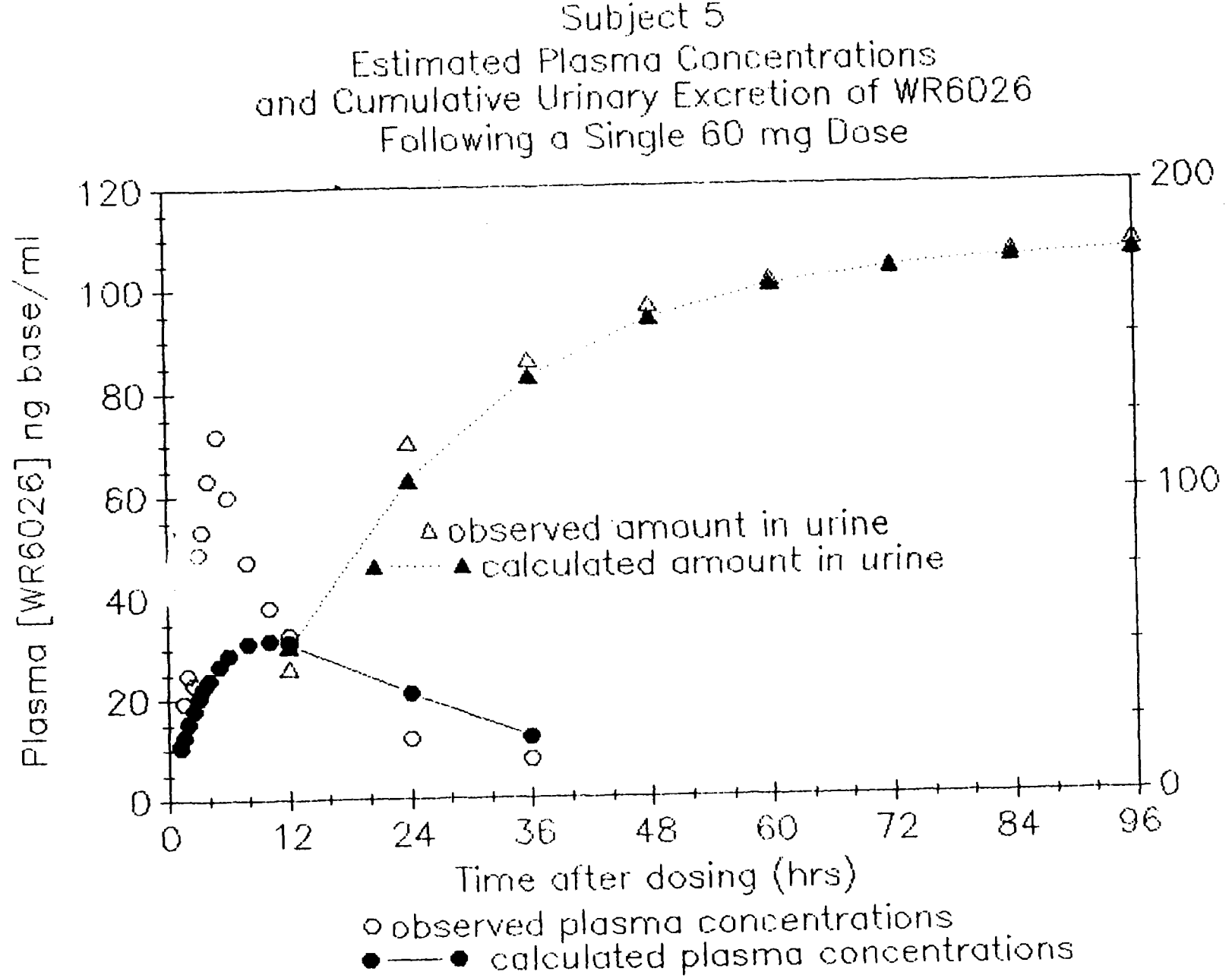

Subject 5
Estimated Plasma Concentrations
and Cumulative Urinary Excretion of WR6026
Following a Single 60 mg Dose
Plasma [WR6026] ng base/ml
Cumulative Amount of WR6026
Excreted in the Urine (ug)
Time after dosing (hrs)
observed amount in urine
calculated amount in urine
observed plasma concentrations
calculated plasma concentrations
0
20
40
60
80
100
120
0
100
200
0
12
24
36
48
60
72
84
96

Figure 21

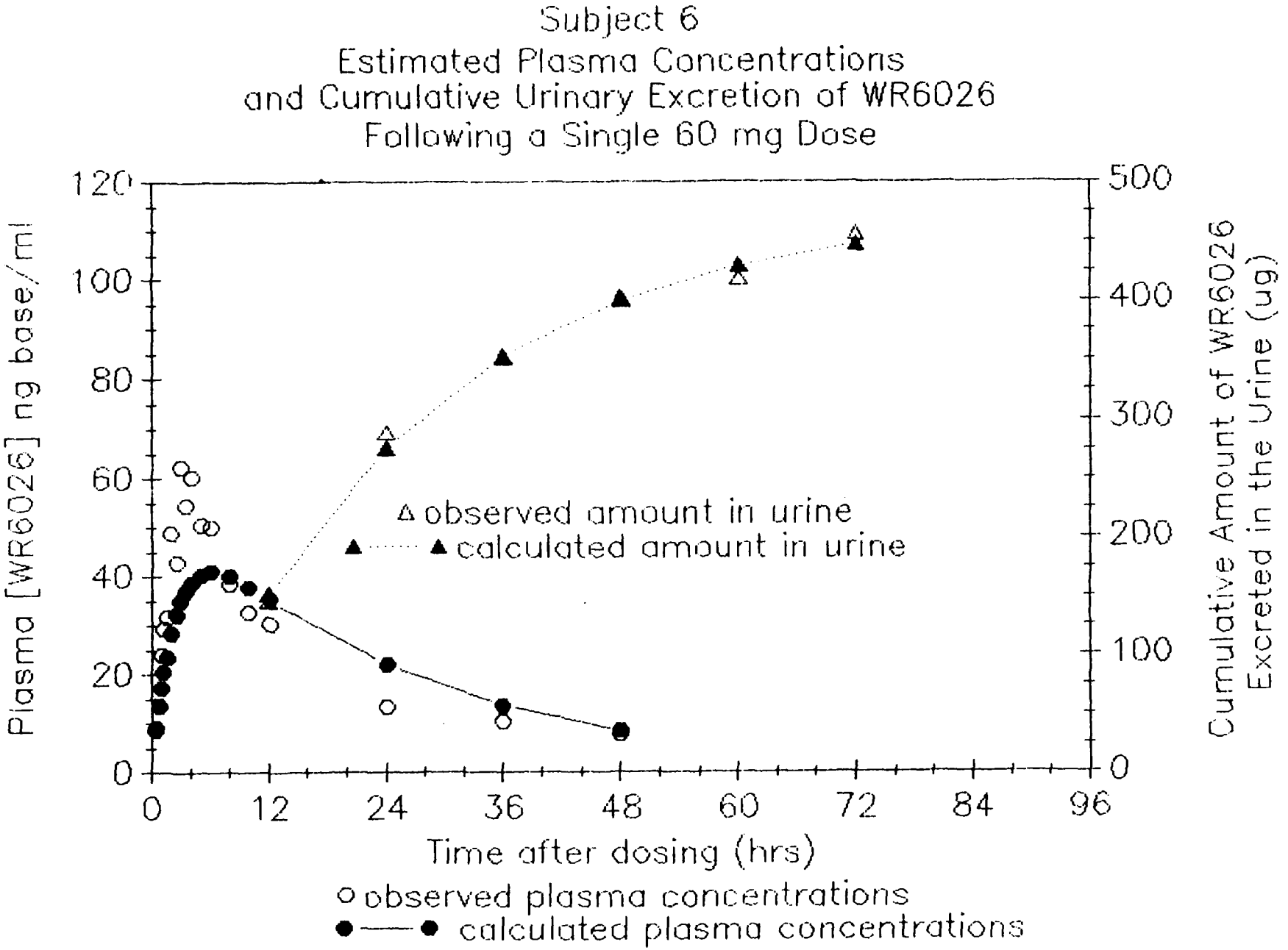

Subject 6
Estimated Plasma Concentrations
and Cumulative Urinary Excretion of WR6026
Following a Single 60 mg Dose
Plasma [WR6026] ng base/ml
Cumulative Amount of WR6026
Excreted in the Urine (ug)
Time after dosing (hrs)
observed amount in urine
calculated amount in urine
observed plasma concentrations
calculated plasma concentrations
0
20
40
60
80
100
120
0
100
200
300
400
500
0
12
24
36
48
60
72
84
96

Figure 22

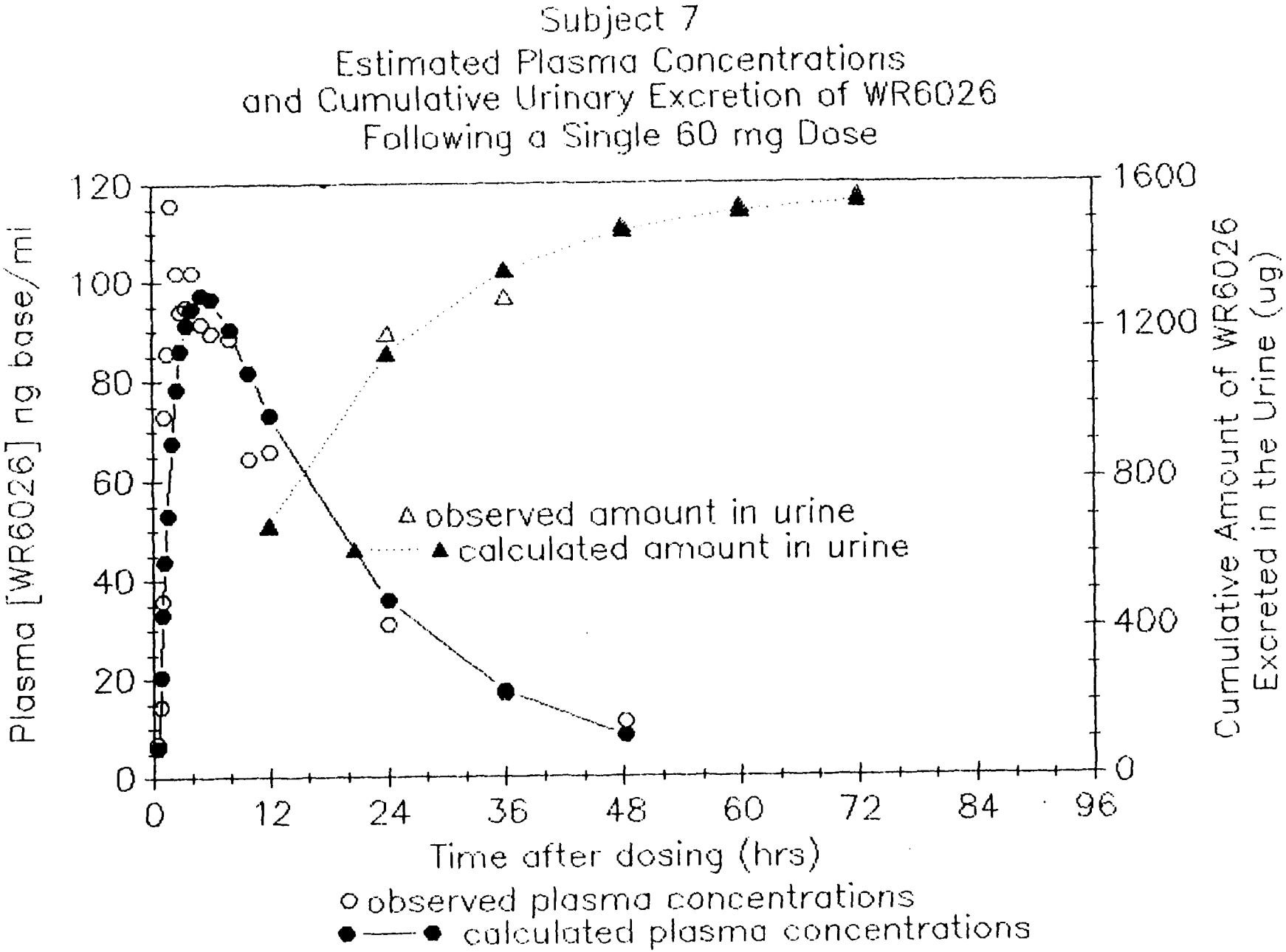
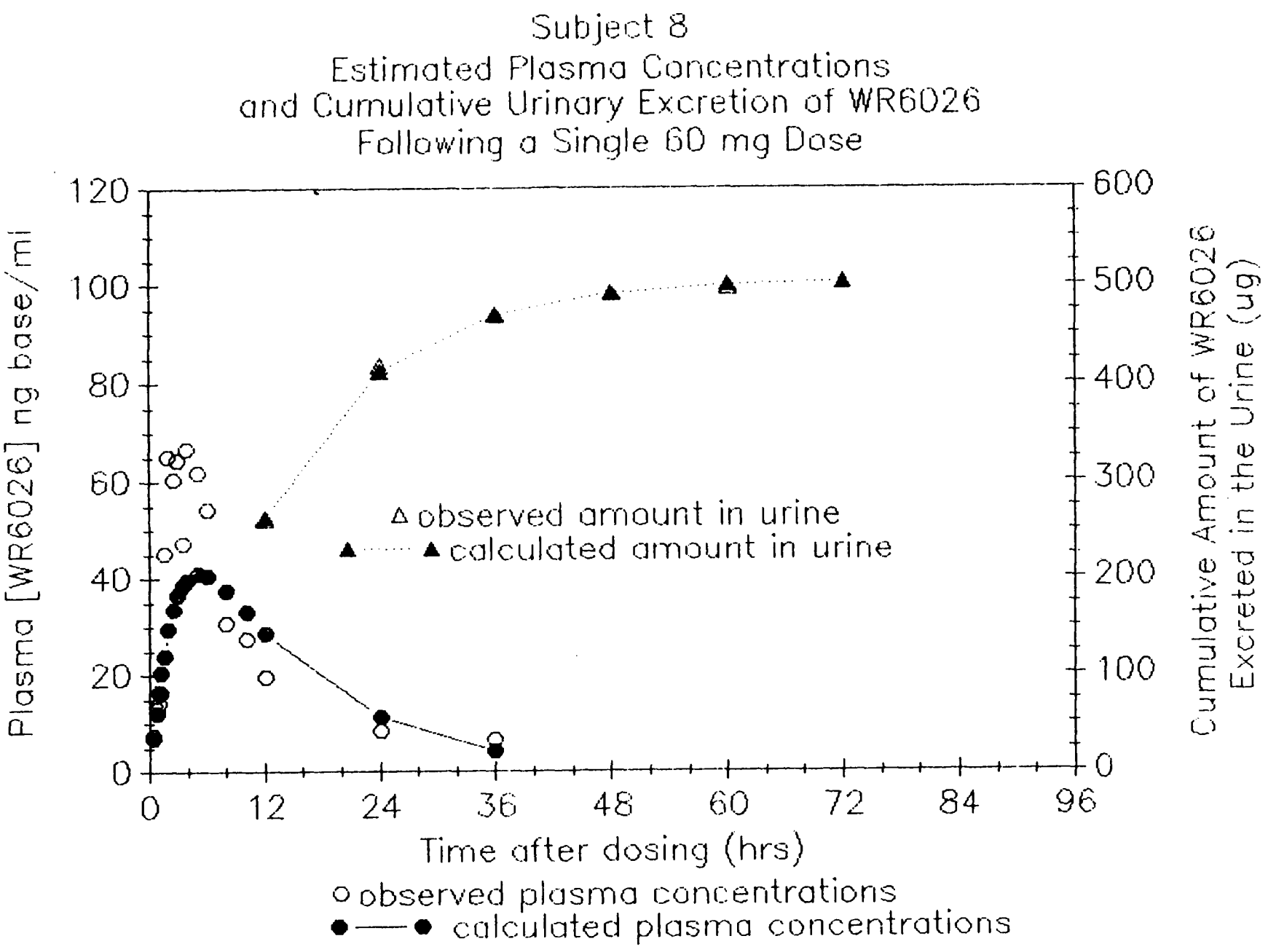

Subject 7
Estimated Plasma Concentrations
and Cumulative Urinary Excretion of WR6026
Following a Single 60 mg Dose
Plasma [WR6026] ng base/ml
Cumulative Amount of WR6026
Excreted in the Urine (ug)
Time after dosing (hrs)
observed amount in urine
calculated amount in urine
observed plasma concentrations
calculated plasma concentrations
0
20
40
60
80
100
120
0
400
800
1200
1600
0
12
24
36
48
60
72
84
96

Figure 23


Subject 8
Estimated Plasma Concentrations
and Cumulative Urinary Excretion of WR6026
Following a Single 60 mg Dose
Plasma [WR6026] ng base/ml
Cumulative Amount of WR6026 Excreted in the Urine (ug)
Time after dosing (hrs)
0
12
24
36
48
60
72
84
96
0
20
40
60
80
100
120
0
100
200
300
400
500
600
△ observed amount in urine
▲ calculated amount in urine
○ observed plasma concentrations
● — ● calculated plasma concentrations

APPENDIX A
Study Flow Chart

DAY	HOUR	APPROXIMATE TIME	PROCEDURE
1	-46	10:00 a.m.	Subject admitted to unit. Sign consent form. Blood tests: CBC with differential SMA 6 SMA 12 LDH, CK Urinalysis
2	-24	8:00 a.m.	Subject begins 12-hour urine collection.
	-12	8:00 p.m.	Subject concludes 12-hour urine collection, begins another 12-hour urine collection.
	-8	12:00 a.m.	NPO
3	-1	7:00 a.m.	Insert heparin lock for blood sampling.
	-0.5	7:30 a.m.	Electrocardiogram
	0	8:00 a.m.	Subject concludes 12-hour urine collection, begins another 12-hour urine collection. Blood tests: CBC with differential SMA6 SMA12 LDH,CK Methemoglobin level Blood for WR 6026 level. Subject takes four 15 mg capsules of WR 6026.
	0.25	8:15 a.m.	Blood for WR 6026 level
	0.5	8:30 a.m.	Blood for WR 6026 level
	0.75	8:45 a.m.	Blood for WR 6026 level
	1.0	9:00 a.m.	Blood for WR 6026 level
	1.25	9:15 a.m.	Blood for WR 6026 level
	1.5	9:30 a.m.	Blood for WR 6026 level

DAY	HOUR	APPROXIMATE TIME	PROCEDURE
3 (cont)	2.0	10:00 a.m.	Blood for WR 6026 level
	2.5	10:30 a.m.	Blood for WR 6026 level
	3.0	11:00 a.m.	Blood for WR 6026 level
	3.5	11:30 a.m.	Blood for WR 6026 level
	4.0	12:00 p.m.	Blood for WR 6026 level. Subject may resume eating. Electrocardiogram
	5.0	1:00 p.m.	Blood for WR 6026 level
	6.0	2:00 p.m.	Blood for WR 6026 level
	8.0	4:00 p.m.	Blood for WR 6026 level
	10.0	6:00 p.m.	Blood for WR 6026 level
	12.0	8:00 p.m.	Blood for WR 6026 level. Subject concludes 12-hour urine collection, begin another 12-hour urine collection.
4	24.0	8:00 a.m.	Blood for WR 6026 level. Subject concludes 12-hour urine collection, begins another 12-hour urine collection. Blood tests: CBC with differential Methemoglobin level SMA 6 SMA 12 Lipid profile LDH, CK Electrocardiogram
	36.0	8:00 p.m.	Blood for WR 6026 level. Subject concludes 12-hour urine collection, begins another 12-hour urine collection.

DAY	HOUR	APPROXIMATE TIME	PROCEDURE
5	48.0	8:00 a.m.	Blood for WR 6026 level. Subject concludes 12-hour urine collection, begins another 12-hour urine collection. Blood tests: CBC with differential Methemoglobin level SMA 6 SMA 12 Lipid profile LDH, CK Electrocardiogram
	60.0	8:00 p.m.	Blood for WR 6026 level. Subject concludes 12-hour urine collection, begins another 12-hour urine collection.
6	72.0	8:00 a.m.	Blood for WR 6026 level. Subject concludes 12-hour urine collection, begins another 12-hour urine collection.
	84.0	8:00 p.m.	Blood for WR 6026 level. Subject concludes 12-hour urine collection, begins another 12-hour urine collection.
7	96.0	8:00 a.m.	Blood for WR 6026 level. Subject concludes 12-hour urine collection, begins another 12-hour urine collection. Blood tests: CBC with differential Methemoglobin level SMA 6 SMA 12 Lipid profile LDH, CK Electrocardiogram
	98.0	10:00 a.m.	Urinalysis Discharge from unit.

Form C (Revised 9/85)
J.H.U.M.S.

APPENDIX B

CLINICAL INVESTIGATION CONSENT FORM
The Johns Hopkins Medical Institutions

Patient I.D. Plate

Title of Research Project: Single-Dose Absorption and Pharmacokinetics of WR 6026 Hydrochloride in Healthy Subjects

Explanation of Research Project to Subject:

You are invited to participate in a study of a drug called WR 6026. WR 6026 is not a licensed drug and therefore is considered investigational. This is a drug used to treat an infection called leishmaniasis which usually occurs in tropical countries and is caused by a parasite. WR 6026 has shown promise as an effective drug to treat this infection. The purpose of this project is to see how healthy volunteers absorb the drug after it is given by mouth, how long the drug stays in the bloodstream, and what byproducts of drug metabolism are eliminated in the urine.

If you agree to join the study you will be hospitalized for six days. You will collect all urine for analysis starting on the second hospital day. On the third hospital day you will take twelve 5 mg capsules of WR 6026 for a total of 60 mg. Following drug administration repeated blood samples will be taken by means of a "heparin lock," a device like an intravenous catheter that stays in your vein and allows blood to be removed without sticking a new needle through the skin each time. A total of 24 blood samples, each less than one tablespoon, will be removed for analysis over the four days after the drug is given. In combination with blood specimens taken before and after the drug is given to monitor its safety, the total amount of blood to be removed for this project is less than one pint. This is less than the amount routinely donated at a blood bank.

We believe that the risks involved with this study are small. When given to animals in large doses for long periods, WR 6026 has caused changes in the kidney, gallbladder, liver, spleen, lungs and heart. In this project however, a much smaller dose for body weight will be given and it is given only once. Healthy human subjects in the 1940's were given WR 6026 for two weeks at a daily dose one half as much as in this project, and they developed only minimal changes in blood tests and EKG but no symptoms. More recently, healthy volunteers have taken single doses of WR 6026, including two who took the same amount you will take in this project, and no symptoms or laboratory abnormalities were seen. The chance of your clinical laboratory tests being abnormal is small. However, if your clinical laboratory tests on Day 7 are abnormal, you will be invited to return for follow-up clinical testing on Day 13 and weekly thereafter until the tests become normal or an alternative explanation is determined. A risk of having a heparin lock for blood withdrawal is the possible discomfort of swelling, soreness and bruising.

Benefits to you for participation in this study are primarily financial, but another potential asset is the comprehensive medical evaluation which accompanies this project, the records of which will be available in the future. If WR 6026 is found to be well absorbed and safe, then it can be studied further to see if it is a better form of therapy for the parasite infection than current drugs.

You are under no obligation to participate in this project. Should you decide not to participate or should you decide to withdraw during the course of the project, your future care at Hopkins will not be affected. You will be paid by check for the proportion of the study which you have completed at the time of withdrawal. Successful completion of the entire study will pay $250. You will be paid by check when you leave the hospital.

Army inspectors may look at the relevant part of your medical record as part of their job to review this study. You are authorized all medical care for injury or disease which is a proximate result of your participation in this research. The medical treatment provided might include, if necessary, laboratory tests, X-rays and other procedures used in diagnosis and treatment. No other compensation for injury is offered.

THIS CONSENT FORM CONTINUES ON THE REVERSE SIDE

Appendix C: Measured Concentrations of WR6026

SUBJ#	FLUID	SCHEDULED TIME hr post dose	ACTUAL TIME hr post dose	NGpML base
1	PL	0.00	-0.23	*
1	PL	0.25	0.25	*
1	PL	0.50	0.50	*
1	PL	0.75	0.75	*
1	PL	1.00	1.00	8.23
1	PL	1.25	1.25	29.8
1	PL	1.50	1.50	26.8
1	PL	2.00	2.00	48.7
1	PL	2.50	2.50	51.0
1	PL	3.00	3.00	53.1
1	PL	3.50	3.50	57.2
1	PL	4.00	4.00	49.2
1	PL	5.00	5.00	44.4
1	PL	6.00	6.00	45.9
1	PL	8.00	8.00	31.4
1	PL	10.00	10.00	32.3
1	PL	12.00	12.00	19.7
1	PL	24.00	24.00	9.8
1	PL	36.00	36.00	*
1	PL	48.00	48.00	*
1	PL	60.00	60.00	*
1	PL	72.00	72.00	*
1	PL	84.00	84.00	*
1	PL	96.00	96.00	*
2	PL	0.00	-0.28	*
2	PL	0.25	0.25	*
2	PL	0.50	0.50	7.26
2	PL	0.75	0.75	30.5
2	PL	1.00	1.00	50.9
2	PL	1.25	1.25	60.3
2	PL	1.50	1.50	75.4
2	PL	2.00	2.00	56.3
2	PL	2.50	2.50	67.0
2	PL	3.00	3.00	59.4
2	PL	3.50	3.50	69.5
2	PL	4.00	4.00	59.8
2	PL	5.00	5.00	57.9
2	PL	6.00	6.00	36.1
2	PL	8.00	8.00	24.8
2	PL	10.00	10.00	21.5
2	PL	12.00	12.00	11.4
2	PL	24.00	24.00	*
2	PL	36.00	36.00	*
2	PL	48.00	48.00	*
2	PL	60.00	58.22	*
2	PL	72.00	72.00	*

* concentration below the detectability limit, 6.44 ng/ml

Appendix C: Measured Concentrations of WR6026

2	PL	84.00	84.00	*
2	PL	96.00	96.00	*
3	PL	0.00	-0.47	*
3	PL	0.25	0.25	*
3	PL	0.50	0.50	*
3	PL	0.75	0.75	*
3	PL	1.00	1.00	7.47
3	PL	1.25	1.25	13.0
3	PL	1.50	1.50	14.7
3	PL	2.00	2.00	28.9
3	PL	2.50	2.50	46.8
3	PL	3.00	3.00	52.5
3	PL	3.50	3.50	36.6
3	PL	4.00	4.00	48.3
3	PL	5.00	5.00	46.6
3	PL	6.00	6.00	39.2
3	PL	8.00	8.00	33.6
3	PL	10.00	10.02	32.5
3	PL	12.00	12.05	26.9
3	PL	24.00	24.00	15.0
3	PL	36.00	36.03	12.0
3	PL	48.00	48.17	*
3	PL	60.00	61.37	*
3	PL	72.00	72.05	*
3	PL	84.00	84.12	*
3	PL	96.00	96.17	*
4	PL	0.00	-0.17	*
4	PL	0.25	0.25	*
4	PL	0.50	0.50	12.9
4	PL	0.75	0.75	18.0
4	PL	1.00	1.00	37.8
4	PL	1.25	1.25	51.2
4	PL	1.50	1.50	59.6
4	PL	2.00	2.00	82.6
4	PL	2.50	2.50	85.6
4	PL	3.00	3.00	68.6
4	PL	3.50	3.50	68.3
4	PL	4.00	4.00	62.8
4	PL	5.00	5.00	75.5
4	PL	6.00	6.00	52.4
4	PL	8.00	8.05	36.8
4	PL	10.00	10.00	37.2
4	PL	12.00	12.00	24.1
4	PL	24.00	24.00	17.6
4	PL	36.00	36.00	8.79
4	PL	48.00	48.00	*

* Concentration below the detectability limit, 6.44 ng/ml

4	PL	60.00	59.45	*
4	PL	72.00	72.03	*
4	PL	84.00	84.08	*
4	PL	96.00	96.00	*
5	PL	0.00	-0.17	*
5	PL	0.25	0.25	*
5	PL	0.50	0.50	*
5	PL	0.75	0.75	*
5	PL	1.00	1.00	*
5	PL	1.25	1.25	10.6
5	PL	1.50	1.50	19.4
5	PL	2.00	2.00	24.9
5	PL	2.50	2.50	23.2
5	PL	3.00	3.03	48.9
5	PL	3.50	3.50	53.3
5	PL	4.00	4.00	63.4
5	PL	5.00	5.00	72.0
5	PL	6.00	6.00	60.1
5	PL	8.00	8.05	47.2
5	PL	10.00	10.02	38.3
5	PL	12.00	12.00	32.7
5	PL	24.00	24.00	12.0
5	PL	36.00	36.00	7.67
5	PL	48.00	48.00	*
5	PL	60.00	61.62	*
5	PL	72.00	72.08	*
5	PL	84.00	84.45	*
5	PL	96.00	96.00	*
6	PL	0.00	-0.08	*
6	PL	0.25	0.25	*
6	PL	0.50	0.50	8.58
6	PL	0.75	0.75	13.7
6	PL	1.00	1.00	24.0
6	PL	1.25	1.25	29.4
6	PL	1.50	1.50	31.6
6	PL	2.00	2.00	49.0
6	PL	2.50	2.50	42.9
6	PL	3.00	3.00	62.3
6	PL	3.50	3.50	54.5
6	PL	4.00	4.00	60.4
6	PL	5.00	5.00	50.5
6	PL	6.00	6.00	50.2
6	PL	8.00	8.00	38.5
6	PL	10.00	10.00	32.6
6	PL	12.00	12.00	30.2
6	PL	24.00	24.08	13.4

* Concentration below the detectability limit, 6.44 ng/ml

Appendix C: Measured Concentrations in WR6026

6	PL	36.00	36.00	10.4
6	PL	48.00	48.00	7.73
6	PL	60.00	60.05	*
6	PL	72.00	72.03	*
6	PL	84.00	84.00	*
6	PL	96.00	96.00	*
7	PL	0.00	-0.53	*
7	PL	0.25	0.25	*
7	PL	0.50	0.50	7.17
7	PL	0.75	0.75	14.4
7	PL	1.00	1.00	35.9
7	PL	1.25	1.25	73.2
7	PL	1.50	1.50	85.7
7	PL	2.00	2.00	116.0
7	PL	2.50	2.50	102.0
7	PL	3.00	3.00	94.1
7	PL	3.50	3.50	94.9
7	PL	4.00	4.00	102.0
7	PL	5.00	5.00	91.4
7	PL	6.00	6.00	89.7
7	PL	8.00	8.00	88.4
7	PL	10.00	10.00	64.6
7	PL	12.00	12.00	66.0
7	PL	24.00	24.00	31.0
7	PL	36.00	36.00	17.0
7	PL	48.00	48.05	11.3
7	PL	60.00	59.30	*
7	PL	72.00	72.08	*
7	PL	84.00	84.08	*
7	PL	96.00	96.05	*
8	PL	0.00	-0.25	*
8	PL	0.25	0.25	*
8	PL	0.50	0.50	7.63
8	PL	0.75	0.75	13.2
8	PL	1.00	1.00	14.2
8	PL	1.25	1.25	16.3
8	PL	1.50	1.50	45.3
8	PL	2.00	2.00	65.2
8	PL	2.50	2.50	60.5
8	PL	3.00	3.00	64.4
8	PL	3.50	3.50	47.3
8	PL	4.00	3.83	66.9
8	PL	5.00	5.00	62.0
8	PL	6.00	6.00	54.2
8	PL	8.00	8.00	30.8
8	PL	10.00	10.02	27.6

* Concentration below the detectability limit, 6.44 ng/ml

Appendix C: Measured Concentrations of WR6026

8	PL	12.00	12.02	19.7
8	PL	24.00	24.00	8.43
8	PL	36.00	36.00	6.60
8	PL	48.00	48.12	*
8	PL	60.00	59.42	*
8	PL	72.00	72.00	*
8	PL	84.00	84.10	*
8	PL	96.00	96.00	*
1	BLD	0.00	-0.28	*
1	BLD	0.25	0.25	*
1	BLD	0.50	0.50	6.69
1	BLD	0.75	0.75	6.84
1	BLD	1.00	1.00	7.79
1	BLD	1.25	1.25	21.3
1	BLD	1.50	1.50	24.7
1	BLD	2.00	2.00	34.7
1	BLD	2.50	2.50	34.2
1	BLD	3.00	3.00	35.1
1	BLD	3.50	3.50	39.1
1	BLD	4.00	4.00	34.8
1	BLD	5.00	5.00	33.6
1	BLD	6.00	6.00	33.1
1	BLD	8.00	8.00	23.6
1	BLD	10.00	10.00	21.5
1	BLD	12.00	12.00	16.9
1	BLD	24.00	24.00	10.2
1	BLD	36.00	36.00	*
1	BLD	48.00	48.00	*
1	BLD	60.00	58.22	*
1	BLD	72.00	72.00	*
1	BLD	84.00	84.00	*
1	BLD	96.00	96.00	*
2	BLD	0.00	-0.28	*
2	BLD	0.25	0.25	*
2	BLD	0.50	0.50	14.8
2	BLD	0.75	0.75	19.2
2	BLD	1.00	1.00	38.9
2	BLD	1.25	1.25	44.7
2	BLD	1.50	1.50	60.9
2	BLD	2.00	2.00	57.7
2	BLD	2.50	2.50	42.2
2	BLD	3.00	3.00	37.0
2	BLD	3.50	3.50	35.7
2	BLD	4.00	4.00	40.1
2	BLD	5.00	5.00	33.7
2	BLD	6.00	6.00	31.0

* Concentration below the detectability limit, 6.44 ng/ml

Appendix C: Measured Concentrations of WR6026

2	BLD	8.00	8.00	25.0
2	BLD	10.00	10.00	12.6
2	BLD	12.00	12.00	10.2
2	BLD	24.00	24.00	*
2	BLD	36.00	36.00	*
2	BLD	48.00	48.00	*
2	BLD	60.00	58.22	*
2	BLD	72.00	72.00	*
2	BLD	84.00	84.00	*
2	BLD	96.00	96.00	*

Appendix D

Table 1*

Precision and Accuracy Data for Analysis of WR 6026, Desethyl WR 6026 and 4-Hydroxymethyl WR 6026 in Human Urine[a]

Amount Added[b] (ng/ml)	Amount Measured[b] (mean ± SD) (ng/ml)	Coefficient of Variation (%)	N
	WR 6026		
17	18 ± 4	27	6
83	84 ± 6	7	10
	Desethyl WR 6026		
16	15 ± 3	20	6
79	83 ± 6	7	8
	4-Hydroxymethyl WR 6026		
15	14 ± 2	14	8
75	75 ± 8	8	10

[a]Data represents a compilation of N separate experiments with 3 replicates of each sample determined for each experiment. A standard curve of 10-500 ng/ml of each compound bracketed spiked unknowns.

[b]Samples were spiked 20 or 100 ng/ml of the salts of each compound. Data shown is corrected for presence of various salt forms of the compounds.

* reproduced from reference #11.

TABLE 2*
4-HYDROXYMETHYL WR6026

NANOGRAMS/ML URINE

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	0	0	0	0	0	0	0	0
0-12	2276	1700	789	1054	651	958	1427	2657
12-24	2316	549	585	1406	1043	1189	1279	2637
24-36	882	636	883	967	771	402	542	1324
36-48	1096	290	346	335	517	665	712	956
48-60	336	257	298	490	291	521	425	406
60-72	579	110	222	374	260	237	168	304
72-84	505	146	382	193	253	266	311	357
84-96	336	118	108	121	144	127	143	268

URINE VOLUME (ML)

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	680	590	1045	735	815	1550	1500	1920
0-12	820	960	1390	510	485	1230	960	1135
12-24	1050	2020	1855	595	1050	1345	1300	1525
24-36	1835	1330	1328	432	802	1960	1605	2590
36-48	830	1630	3130	745	1160	1480	1505	1615
48-60	1750	1426	1695	685	1000	950	1095	2600
60-72	1315	1860	1805	490	1070	1635	1195	1890
72-84	715	1410	1650	1050	750	1600	1565	1860
84-96	790	1720	1720	745	1025	1570	1460	1970

TOTAL EXCRETED/SAMPLE (MICROMOLES)

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0-12	5.2	4.5	3.1	1.5	0.9	3.3	3.8	8.4
12-24	6.8	3.1	3.0	2.3	3.0	4.5	4.6	11.2
24-36	4.5	2.4	3.3	1.2	1.7	2.2	2.4	9.6
36-48	2.5	1.3	3.0	0.7	1.7	2.7	3.0	4.3
48-60	1.6	1.0	1.4	0.9	0.8	1.4	1.3	2.9
60-72	2.1	0.6	1.1	0.5	0.8	1.1	0.6	1.6
72-84	1.0	0.6	1.8	0.6	0.5	1.2	1.4	1.9
84-96	0.7	0.6	0.5	0.3	0.4	0.6	0.6	1.5
TOTAL	24.5	14.0	17.2	7.9	9.8	16.9	17.6	41.3

RATE OF EXCRETION (NANOMOLES/HOUR)

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0-12	433.2	378.8	254.5	124.8	73.[illegible]	273.4	318.0	700.1
12-24	564.4	257.6	252.0	194.2	254.2	371.3	385.9	933.5
24-36	375.6	196.3	272.2	97.0	143.5	182.8	201.9	796.0
36-48	211.1	109.7	251.2	57.9	139.2	228.5	248.8	358.5
48-60	136.7	85.0	117.2	77.9	67.5	114.8	107.9	245.0
60-72	176.6	47.7	93.1	42.5	64.6	89.9	46.5	133.4
72-84	83.9	47.9	146.2	47.2	44.0	98.6	112.9	154.3
84-96	61.7	47.3	43.0	21.0	34.4	46.4	48.6	122.4

* reproduced from reference #11.

TABLE 3*
DESETHYL WR6026

NANOGRAMS/ML URINE

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	0	0	0	0	0	0	0	0
0-12	42	48	20	54	17	23	90	48
12-24	25	11	14	12	24	24	90	51
24-36	10	8	16	24	13	7	2	14
36-48	10	0	8	10	4	7	19	11
48-60	0	0	0	8	0	8	17	0
60-72	0	0	0	3	0	0	8	0
72-84	0	0	0	4	0	0	12	0
84-96	0	0	0	0	0	0	2	0

URINE VOLUME (ML)

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	680	590	1045	735	815	1550	1500	1920
0-12	820	960	1390	510	485	1230	960	1135
12-24	1050	2020	1855	595	1050	1345	1300	1525
24-36	1835	1330	1328	432	802	1960	1605	2590
36-48	830	1630	3130	745	1160	1480	1505	1615
48-60	1750	1426	1695	685	1000	950	1095	2600
60-72	1315	1860	1805	490	1070	1635	1195	1890
72-84	715	1410	1650	1050	750	1600	1565	1860
84-96	790	1720	1720	745	1025	1570	1460	1970

TOTAL EXCRETED/SAMPLE (MICROMOLES)

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0-12	0.09	0.13	0.08	0.08	0.02	0.08	0.24	0.15
12-24	0.07	0.06	0.07	0.02	0.07	0.09	0.33	0.22
24-36	0.05	0.03	0.06	0.03	0.03	0.04	0.01	0.10
36-48	0.02	0.00	0.07	0.02	0.01	0.03	0.08	0.05
48-60	0.00	0.00	0.00	0.02	0.00	0.02	0.05	0.00
60-72	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.00
72-84	0.00	0.00	0.00	0.01	0.00	0.00	0.05	0.00
84-96	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
TOTAL	0.25	0.22	0.28	0.18	0.14	0.26	0.79	0.52

RATE OF EXCRETION (NANOMOLES/HOUR)

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0-12	7.9	10.7	6.5	6.3	1.9	6.6	20.0	12.6
12-24	6.1	5.3	6.0	1.6	5.9	7.4	27.3	18.0
24-36	4.3	2.3	5.0	2.4	2.4	3.3	0.6	8.7
36-48	2.0	0.0	5.5	1.8	1.2	2.5	6.6	4.1
48-60	0.0	0.0	0.0	1.3	0.0	1.7	4.4	0.0
60-72	0.0	0.0	0.0	0.3	0.0	0.0	2.2	0.0
72-84	0.0	0.0	0.0	1.0	0.0	0.0	4.2	0.0
84-96	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.0

* reproduced from reference #11.

Appendix D

TABLE 4*
WR6026

NANOGRAMS/ML URINE

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	0	0	0	0	0	0	0	0
0-12	157	149	148	254	90	119	706	230
12-24	56	20	71	155	70	106	396	103
24-36	25	10	59	61	33	32	61	20
36-48	26	0	18	18	15	34	128	14
48-60	3	0	13	23	8	17	49	2
60-72	9	0	8	20	4	23	24	3
72-84	9	0	17	12	6	0	0	0
84-96	0	0	0	0	3	0	0	0

URINE VOLUME (ML)

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	680	590	1045	735	815	1550	1500	1920
0-12	820	960	1390	510	485	1230	960	1135
12-24	1050	2020	1855	595	1050	1345	1300	1525
24-36	1835	1330	1328	432	802	1960	1605	2590
36-48	830	1630	3130	745	1160	1480	1505	1615
48-60	1750	1426	1695	685	1000	950	1095	2600
60-72	1315	1860	1805	490	1070	1635	1195	1890
72-84	715	1410	1650	1050	750	1600	1565	1860
84-96	790	1720	1720	745	1025	1570	1460	1970

TOTAL EXCRETED/SAMPLE (MICROMOLES)

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0-12	0.38	0.42	0.60	0.38	0.13	0.43	1.97	0.76
12-24	0.17	0.12	0.38	0.27	0.21	0.41	1.50	0.46
24-36	0.13	0.04	0.23	0.08	0.08	0.19	0.29	0.15
36-48	0.06	0.00	0.16	0.04	0.05	0.14	0.56	0.07
48-60	0.01	0.00	0.07	0.05	0.02	0.05	0.16	0.01
60-72	0.04	0.00	0.04	0.03	0.01	0.11	0.08	0.02
72-84	0.02	0.00	0.08	0.04	0.01	0.00	0.00	0.00
84-96	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00
TOTAL	0.82	0.57	1.56	0.87	0.53	1.33	4.57	1.47

RATE OF EXCRETION (NANOMOLES/HOUR)

SAMPLE	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8
-12-0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0-12	31.3	34.7	49.8	31.5	10.6	35.5	164.6	63.5
12-24	14.4	10.0	31.9	22.5	17.8	34.5	125.1	38.3
24-36	11.2	3.1	19.0	6.4	6.3	15.4	23.9	12.5
36-48	5.3	0.0	13.7	3.3	4.2	12.1	46.9	5.6
48-60	1.2	0.0	5.4	3.8	1.9	3.9	13.1	1.2
60-72	3.0	0.0	3.7	2.4	1.1	9.1	7.0	1.5
72-84	1.6	0.0	6.7	3.1	1.1	0.0	0.0	0.0
84-96	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0

* reproduced from reference #11.

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	E = W F M L	01	PROTOCOL:DAMD 17-85-C-5133-03

PROTOCOL

Study Day	Date ddmmmyy	Procedures
	25Jun86	Screening laboratory
	02Jul86	History, Physical Exam
0	05Jul86	Admission
3	07Jul86	Drug Administration

I certify that:

1) I have carefully examined all entries on the data collection forms, consisting of __14__ pages, for subject #__01__.

2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Scott Pitts M.D. 16/Dec/86

Investigator's signature dd/mmm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	E — W F M L	01	PROTOCOL:DAMD 17-85-C-5133-03

MEDICAL HISTORY

Date of evaluation 02/Jul/86 (dd mmm yy)

Examiner Brent G Petty, M.D.

Dr. Brent G Petty (print name)

Date of birth 26/Jan/64 (dd mmm yy)

Age 22 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	½ ppd
Alcohol Use		✓	6 pack/week
Recreational Drug Use		✓	MJ ~ 1 week
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	JHU
Blood or plasma donor	✓		
Prior Surgery		✓	(R knee Surgery p MVA age 6
Eye, ear, nose, throat		✓	No fever) "Sniffles" x 1 hx p hay fever
Endocrine(diabetes,thyroid)	✓		
C-V (heart murmur,HBP)	✓		
Pulmonary (cough,asthma)	✓		
Hepatitis,gastro-intestinal	✓		
Genito-urinary		✓	Rx'd c injection Lues 3-4 years ago
Musculoskeletal	✓		
Neuropsychiatric	✓		
Other			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	E W F M L	01	PROTOCOL:DAMD 17-85-C-5133-03

PHYSICAL EXAMINATION
Date 02/Jul/86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
35.4 C	042/min	12/min	108/58	176.0	73.5

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	lymphoid excrescence post pharynx
Chest, lungs	(By)	✓	right chest slightly deformed from bony and/or soft tissue (eg, muscle) at 2nd costochondral articulation, first noted 1982
Heart	✓		
Abdomen	✓		
Genitalia			Not done
Rectal			Not done
Extremities	✓		
Skin		✓	tattoos (L) ant chest + (L) upper arm + (L) lo...
Neurologic	✓		

CHEST X-RAY
Date 22/Jul/86

NORMAL	X	ABNORMAL		Describe abnormalities:

Examiner Brent C Pethy

Dr Brent C Pethy
print name

7.29.86 JB

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	E — W F M L	01	PROTOCOL: DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	07Jul86	0802	N.A.	PO	

DOSAGE (total) 60 mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	Methemoglobin %
	0	07Jul86	0748	0748	*	0%
	0.25	07Jul86	0817	0817	*	
	0.50	07Jul86	0832	0832	*	
	0.75	07Jul86	0847	0847	*	
	1.0	07Jul86	0902	0902	8.23	
	1.25	07Jul86	0917	0917	29.8	
	1.50	07Jul86	0932	0932	26.8	
	2.0	07Jul86	1002	1002	48.7	
	2.5	07Jul86	1032	1032	51.0	
	3.0	07Jul86	1102	1102	53.1	
	3.5	07Jul86	1132	1132	57.2	
	4.0	07Jul86	1202	1202	49.2	
	5.0	07Jul86	1302	1302	44.4	
	6.0	07Jul86	1402	1402	45.9	4%
	8.0	07Jul86	1602	1602	31.4	
	10.0	07Jul86	1802	1802	32.3	
	12.0	07Jul86	2002	2002	19.7	

7.29.86
PB

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	F E M — L W	01	PROTOCOL:DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	07Jul86	0802	N.A.	PO	

* Below Assay Sensitivity

DOSAGE (total) 60 mg

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	Methemoglobin %
	24.0	08Jul86	0802	0802	9.80	0.7
	36.0	08Jul86	2002	2002	*	
	48.0	09Jul86	0802	0802	*	0.7
	60.0	09Jul86	2002	2002	*	
	72.0	10Jul86	0802	0802	*	
	84.0	10Jul86	2002	2002	*	
	96.0	11Jul86	0802	0802	*	1.0

7-29-86

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	E — W F M L	01	PROTOCOL:DAMD 17-85-C-5133-03

URINE CONCENTRATIONS

STUDY:WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	07Jul86	0802	NA	PO	

DOSAGE (total) 60 mg

URINE CONCENTRATIONS

Sample No.	Scheduled Collection Time (hours)	Start Collection		End Collection		Total Volume (ml)	[WR6026] mg
		ddmmmyy	0-2400	ddmmmyy	0-2400		
U01	-24 TO -12	06Jul86	0800	06Jul86	2000	1315	—
U02	-12 TO 0	06Jul86	2000	07Jul86	0800	680	0
U03	0 TO 12	07Jul86	0800	07Jul86	2000	820	0.101792
U04	12 TO 24	07Jul86	2000	08Jul86	0800	1650	0.04935
U05	24 TO 36	08Jul86	0800	08Jul86	2000	1835	0.038535
U06	36 TO 48	08Jul86	2000	09Jul86	0800	830	0.01826
U07	48 TO 60	09Jul86	0800	09Jul86	2000	1750	0.004025
U08	60 TO 72	09Jul86	2000	10Jul86	0800	1315	0.010388
U09	72 TO 84	10Jul86	0800	10Jul86	2000	715	0.005648
U10	84 TO 96	10Jul86	2000	11Jul86	0800	790	0
*							✓

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	E - W F M L	01	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Screen -	Predrug 1	Predrug 2 3	Postdrug 4	Postdrug 5	Day
	25Jun86 ddmmmyy	05Jul86 ddmmmyy	07 ~~06~~Jul86 ddmmmyy	08Jul86 ddmmmyy	09Jul86 ddmmmyy	Date
NA:135-148 MEQ/L	142	138	142	139	142	
K:3.5-5.0 MEQ/L	3.9	3.8	4.6	4.3	4.1	
CL:96-109 MEQ/L	110	107	104	105	101	
CO2:24-30 MEQ/L	24	22	23	24	25	
SUN:12-25 MG/DL	16	26	12	13	14	
CREAT:0.4-1.5 MG/DL	1.0	1.1	1.0	1.0	1.0	
GLU:70-115 MG/DL	96	85	82	88	91	
T.BILI:0.3-1.2MG/DL	1.4	1.3	1.6	1.1	1.3	
D.BILI:0.1-0.4MG/DL	0.1	0.2	0.2	0.1	0.1	
CA:9.0-11.0 MG/DL	9.5	9.1	9.3	9.4	10.1	
PO4:3.0-4.5 MG/DL	4.4	4.1	4.4	4.6	5.2	
URIC A:4.2-8.8MG/DL	5.5	5.8	4.1	4.1	4.3	
T. PROT:6.0-8.5G/DL	6.7	6.7	6.4	6.3	7.5	
ALB. :3.2-5.3 G/DL	—	4.6	4.5	4.5	ND	
AST:0-35 IU/L	19	36	16	25	31	
ALT:0-30 IU/L	10	15	15	14	21	
ALK PHOS:0-95 IU/L	44	52	45	42	47	
CHOL:151-268 MG/DL	203	201	228 ~~[illegible]~~	205 ~~[illegible]~~	247 ~~[illegible]~~	
LDH:0-200 IU/L	—	183	150	139	137	
CPK:0-160 U/L(male)	—	712	434	557	247	
TG:20-190 MG/DL	54	—	66	58	69	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	E F — M W L	01	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Postdrug 7 Day 11Jul86 Date ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
NA:135-148 MEQ/L	140				
K:3.5-5.0 MEQ/L	4.3				
CL:96-109 MEQ/L	99				
CO2:24-30 MEQ/L	29				
SUN:12-25 MG/DL	18				
CREAT:0.4-1.5 MG/DL	1.0				
GLU:70-115 MG/DL	80				
T.BILI:0.3-1.2MG/DL	1.3				
D.BILI:0.1-0.4MG/DL	0.6				
CA:9.0-11.0 MG/DL	10.5				
PO4:3.0-4.5 MG/DL	4.9				
URIC A:4.2-8.8MG/DL	4.8				
T. PROT:6.0-8.5G/DL	7.6				
ALB.:3.2-5.3 G/DL	5.1				
AST:0-35 IU/L	27				
ALT:0-30 IU/L	13				
ALK PHOS:0-95 IU/L	42				
CHOL:151-268 MG/DL	~~217~~ 255				
LDH:0-200 IU/L	217				
CPK:0-160 U/L(male)	ND				
TG:20-190 MG/DL	ND.				

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	E — W F M L	01	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Screen –	Predrug 1	Predrug 3	Postdrug 4	Postdrug 5	Day
		25Jun86	05Jul86	07Jul86	08Jul86	09Jul86	Date
		ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
WBC	4500-11000	5600	6200	5800	5500	5000	
RBC	4.50-5.90	4.80	4.65	5.10	4.90	5.10	
Hgb	13.9-16.3	14.4	13.7	15.0	14.7	15.4	
PCV	41.0-53.0	42.4	41.0	45.2	43.8	45.4	
Plt	150-350	304	281	271	264	285	
Bands	2-6%	0	5	—	2	—	
Polys	31-76%	54	45	50	42	51	
Eos	1-4%	2	1	0	5	4	
Bas		0	1	0	2	0	
Lymphs	24-44%	40	36	36	35	38	
Atyp Lym		2	1	1	1	0	
Monos	2-11%	2	11	13	13	4	
Other		0	0	0	0	0	
Methem:		02Jul86 0.3%		0.0	0.3	0.7	
G-6-PD	7.4-9.4	6.9					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	F M L	01	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Postdrug 7 Day / Date 11JUL86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
WBC	4500-11000	7000				
RBC	4.50-5.90	5.07				
Hgb	13.9-16.3	15.2				
PCV	41.0-53.0	459				
Plt	150-350	302				
Bands	2-6%	4				
Polys	31-76%	45				
Eos	1-4%	2				
Bas		0				
Lymphs	24-44%	37				
Atyp Lym		0				
Monos	2-11%	12				
Other		0				
methem		1.0				
G-6-PD	7.4-9.4					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	E — W F M L	01	PROTOCOL: DAMD 17-85-C-5133-03

URINALYSIS VALUES

Laboratory: JOHNS HOPKINS HOSPITAL

		Screen –	Predrug 1	4	Postdrug 5	7
		02Jul86 ddmmmyy	05Jul86 ddmmmyy	08Jul86 ddmmmyy	09Jul86 ddmmmyy	11Jul86 ddmmmyy
Sp. Gr.		1.034	1.032	1.016	1.017	1.034
pH		6.0	6.5	7.0	7.0	7.0
Protein		~~Neg~~ ~~Trace~~ ~~Neg~~ (3+)	Neg	~~Neg~~ ~~Trace~~ (2+)	~~Neg~~ ~~Trace~~ ~~Neg~~ (2+)	~~Neg~~ ~~Trace~~ ~~Neg~~ (3+)
Glucose		Neg	Neg	Neg	Neg	Neg
Ketones		Neg	Neg	Neg	Neg	Neg
Bili.		Neg	Neg	Neg	Neg	Neg
Occ. Bld.		Neg	Neg	Neg	Neg	Neg
Cast/lpf		0	0	0	0	0
WBC/hpf		0	0	0	0	0
RBC/hpf		0	0	0	0	0
Epi./hpf		0	0	0	0	0-1
Crys/hpf		0	0	0	0	0
Bact/hpf		0	0	0	0	0

ELECTROCARDIOGRAM

	Date ddmmmyy	Time 0-2400	NORMAL check	ABNORMAL check	Describe abnormalities
Screen	02July86	1130		✓	non specific T wave changes, possibly 2° to bad placement
	07July86	0725		✓	non-specific T wave changes
	07Jul86	1157		✓	non specific T wave Δ, 2° bad placement
	08Jul86	0750	✓		
	09Jul86	0750	✓		
11	Jul86	0750	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	E M W F M L	C1	PROTOCOL:DAMD 17-85-C-5133-03

ADVERSE EXPERIENCES

check if none occurred ☒

#	ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
1	Increase in LDH	11 JUL 92 dd mmm yy 0800 (0-2400)	dd mmm yy 11 July 1992 (0-2400)	☒ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☒ POSS. ☐ DEF. NOT ☐ UNKNOWN	☒ None ☐ Treatment ☐ Stop test drug
#		dd mmm yy (0-2400)	dd mmm yy (0-2400)	☐ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☐ DEF. NOT ☐ UNKNOWN	☐ None ☐ Treatment ☐ Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	F M L	01	PROTOCOL:DAMD 17-85-C-5133-03

OUTCOME
(To be completed for all subjects)

☒	Protocol completed	11Jul86 ddmmmyy
☐	Premature termination of protocol	_____ ddmmmyy

REASON FOR PREMATURE TERMINATION
(Check appropriate category)

- ☐ Adverse Experience
- ☐ Died During Study
- ☐ Failure To Return For Follow-up
- ☐ Did Not Cooperate
- ☐ Protocol Violation
- ☐ Entry Violation
- ☐ Intercurrent Illness
- ☐ Administrative/Other

If terminated early, explain briefly:

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	E — N F M L	01	PROTOCOL:DAMD 17-85-C-5133 03

CONCOMITANT MEDICATIONS

DRUG NAME	TOTAL DAILY DOSE	DATE STARTED	DATE STOPPED
heparin flush	300 - 1000 units	07 Jul 86	10 Jul 86

COMMENTS
(please date and sign all comments)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

PROTOCOL

Study Day	Date ddmmmyy	Procedures
	09Jul86	Screening laboratory
	10Jul86	History, Physical Exam
0	~~15~~ 12Jul86	Admission
3	~~07~~ 14Jul86	Drug Administration

I certify that:

1) I have carefully examined all entries on the data collection forms, consisting of __14___ pages, for subject #__02___.

2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent L Lietman M.D. — 16/Dec/86

Investigator's signature — dd/mmm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

MEDICAL HISTORY

Date of evaluation 10/Jul/86 (dd mmm yy)

Examiner Dr. B.G. Athy (print name)

Date of birth 13/Aug/57 (dd mmm yy)

Age 28 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	½ PPD
Alcohol Use	✓		Quit 6 months ago
Recreational Drug Use	✓		Quit 6 months ago
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	Johns Hopkins Hospital
Blood or plasma donor		✓	August 1985
Prior Surgery		✓	Appy 1978, T+A 1975
Eye, ear, nose, throat	✓		
Endocrine(diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	GC-1978, Lues 1975, Rx'd PCN
Musculoskeletal	✓		
Neuropsychiatric	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

PHYSICAL EXAMINATION
Date 10/Jul/86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
35.9 C	64/min	14/min	108/72	178.0	73.6

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		Neck-Shotty nodes
EENT	✓		throat minimal lymphoid tissue in fossa, p-s
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			Not done
Rectal			not done
Extremities	✓		
Skin		✓	Appy scar, antebubital scars, forehead scar
Neurologic	✓		

CHEST X-RAY
Date 09/Jan/86

NORMAL	X	ABNORMAL		Describe abnormalities:

Examiner Brian G Petty
Dr. B.G. PeHy
print name

7.29.86

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	R L H F M L	02	PROTOCOL: DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	~~07~~ 14 Jan 86	0802	N.A.	PO	

DOSAGE (total) 60 mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemoglobin *~~
	0	14 Jul 86	0745	0745	*	
	0.25	14 Jul 86	0817	0817	*	
	0.50	14 Jul 86	0832	0832	7.26	
	0.75	14 Jul 86	0847	0847	30.5	
	1.0	14 Jul 86	0902	0902	50.9	
	1.25	14 Jul 86	0917	0917	60.3	
	1.50	14 Jul 86	0932	0932	75.4	
	2.0	14 Jul 86	1002	1002	56.3	
	2.5	14 Jul 86	1032	1032	67.0	
	3.0	14 Jul 86	1102	1102	59.4	
	3.5	14 Jul 86	1132	1132	69.5	
	4.0	14 Jul 86	1202	1202	59.8	
	5.0	14 Jul 86	1302	1302	57.9	
	6.0	14 Jul 86	1402	1402	36.1	
	8.0	14 Jul 86	1602	1602	24.8	
	10.0	14 Jul 86	1802	1802	21.5	
	12.0	14 Jul 86	2002	2002	11.4	

J.2943

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R/F L/M H/L	02	PROTOCOL:DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	14Jul86	0802	NA.	PO	

* Below Assay Sensitivity

DOSAGE (total) 60 mg

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemoglobin %~~
	24.0	15Jul86	0802	0802	*	
	36.0	15Jul86	2002	2002	*	
	48.0	16Jul86	0802	0802	*	
	60.0	16Jul86	2002	2015	*	
	72.0	17Jul86	0802	0802	*	
	84.0	17Jul86	2002	2002	*	
	96.0	18Jul86	0802	0802	*	

.29.86 75

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

URINE CONCENTRATIONS

STUDY:WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	14Jul86	0802	N.A.	PO	

DOSAGE (total) 60 mg

URINE CONCENTRATIONS

Sample No.	Scheduled Collection Time (hours)	Start Collection ddmmmyy	Start Collection 0-2400	End Collection ddmmmyy	End Collection 0-2400	Total Volume (ml)	[WR6026] mg
U01	-24 TO -12	13Jul86	0800	13Jul86	2000	1355	~~0~~
U02	-12 TO 0	13Jul86	*	13Jul86	0800	95.5	0 ~~[illegible]~~
U03	0 TO 12	14Jul86	0800	14Jul86	2000	960	0.11904 ~~0.03434~~
U04	12 TO 24	14Jul86	2000	15Jul86	0800	3020	0.03434 ~~0.01064~~
U05	24 TO 36	15Jul86	0800	15Jul86	2002	1330	0.01064
U06	36 TO 48	15Jul86	2002	16Jul86	0802	1630	0
U07	48 TO 60	16Jul86	0802	16Jul86	2000	1420	0
U08	60 TO 72	16Jul86	2000	17Jul86	0800	1860	0
U09	72 TO 84	17Jul86	0800	17Jul86	2000	1410	0
U10	84 TO 96	17Jul86	2000	18Jul86	0800	1730	0

* Spot urine because pt. failed to accurately save urine from 13 July 1986 at 2000.

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Screen -	Predrug 1	Predrug 2	Postdrug 4	Postdrug 5	Day
	09Jul86 ddmmmyy	12Jul86 ddmmmyy	14Jul86 ddmmmyy	15Jul86 ddmmmyy	16Jul86 ddmmmyy	Date
NA:135-148 MEQ/L	144	144	139	145	140	
K:3.5-5.0 MEQ/L	4.1	3.9	4.3	4.1	4.5	
CL:96-109 MEQ/L	111	113	106	104	106	
CO2:24-30 MEQ/L	25	19	22	25	22	
SUN:12-25 MG/DL	14	13	10	12	15	
CREAT:0.4-1.5 MG/DL	1.3	1.4	1.1	1.2	1.2	
GLU:70-115 MG/DL	60	84	70	77	76	
T.BILI:0.3-1.2MG/DL	0.7	0.3	0.6	0.5	0.4	
D.BILI:0.1-0.4MG/DL	0.0	0.0	0.1	0.1	0.2	
CA:9.0-11.0 MG/DL	9.4	8.7	9.4	10.1	9.3	
PO4:3.0-4.5 MG/DL	4.1	3.1	3.7	3.5	4.0	
URIC A:4.2-8.8MG/DL	7.5	5.4	5.0	5.1	5.7	
T. PROT:6.0-8.5G/DL	6.3	5.8	6.4	6.7	6.5	
ALB.:3.2-5.3 G/DL	ND	3.8	3.9	4.4	4.2	
AST:0-35 IU/L	34	33	24	24	33	
ALT:0-30 IU/L	16	17	19	22	20	
ALK PHOS:0-95 IU/L	43	52	51	46	44	
CHOL:151-268 MG/DL	140	125	167	174	164	
LDH:0-200 IU/L	158	144	145	122	131	
CPK:0-160 U/L(male)	570	635	296	283	245	
TG:20-190 MG/DL	69	~~[illegible]~~ W.D.	62	68	45	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Postdrug 7 18JUL86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	Day Date
NA:135-148 MEQ/L	141					
K:3.5-5.0 MEQ/L	4.3					
CL:96-109 MEQ/L	103					
CO2:24-30 MEQ/L	27					
SUN:12-25 MG/DL	14					
CREAT:0.4-1.5 MG/DL	1.3					
GLU:70-115 MG/DL	71					
T.BILI:0.3-1.2MG/DL	0.6					
D.BILI:0.1-0.4MG/DL	0.1					
CA:9.0-11.0 MG/DL	10.2					
PO4:3.0-4.5 MG/DL	4.2					
URIC A:4.2-8.8MG/DL	5.5					
T. PROT:6.0-8.5G/DL	7.3					
ALB.:3.2-5.3 G/DL	4.5					
AST:0-35 IU/L	29					
ALT:0-30 IU/L	27					
ALK PHOS:0-95 IU/L	47					
CHOL:151-268 MG/DL	183					
LDH:0-200 IU/L	394					
CPK:0-160 U/L(male)	272					
TG:20-190 MG/DL	62					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Screen -	Predrug 1	Predrug 3	Postdrug 4	Postdrug 5	Day
		09Jul86	12Jul86	14Jul86	15Jul86	16Jul86	Date
		ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
WBC	4500-11000	8800	7800	7800	7700	7700	
RBC	4.50-5.90	4.65	4.31	4.93	5.06	4.99	
Hgb	13.9-16.3	14.5	13.4	15.6	15.5	15.6	
PCV	41.0-53.0	43.2	39.9	45.4	48.3	47.1	
Plt	150-350	253	238	272	309	274	
Bands	2-6%	1	2	6	4	1	
Polys	31-76%	45	45	49	38	49	
Eos	1-4%	3	1	1	2	4	
Bas		0	0	1	0	0	
Lymphs	24-44%	41	46	32	45	40	
Atyp Lym		0	0	0	0	0	
Monos	2-11%	10	6	11	11	6	
Other		0	0	0	0	0	
		10Jul86					
Methem.		0.1		0.0/0.1	0.0	0.0	
G-6-PD	7.4-9.4	7.8					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Postdrug 7 18Jul86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
		Day				
		Date				
WBC	4500-11000	8600				
RBC	4.50-5.90	5.04				
Hgb	13.9-16.3	15.6				
PCV	41.0-53.0	46.9				
Plt	150-350	288				
Bands	2-6%	3				
Polys	31-76%	48				
Eos	1-4%	0				
Bas		1				
Lymphs	24-44%	40				
Atyp Lym		0				
Monos	2-11%	8				
Other		0				
Methem.		0.5				
G-6-PD	7.4-9.4					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

URINALYSIS VALUES

Laboratory: JOHNS HOPKINS HOSPITAL

		Screen -	Predrug 1	4	Postdrug 5	7
		10Jul86 ddmmmyy	12Jul86 ddmmmyy	15Jul86 ddmmmyy	_____ ddmmmyy	18Jul86 ddmmmyy
Sp.Gr.		1.023	1.023	1.011		1.017
pH		6.0	5.0	6.0		6.5
Protein		Neg	Neg	Neg		Neg
Glucose		Neg	Neg	Neg		Neg
Ketones		Neg	Neg	Neg		Neg
Bili.		Neg	Neg	Neg		Neg
Occ.Bld.		Neg	Neg	Neg		Neg
Cast/lpf		0	0	0		0
WBC/hpf		0	0	0		0-1
RBC/hpf		0	0	0		0
Epi./hpf		0	0	0		0
Crys/hpf		0	0	0		0
Bact/hpf		0	0	0		0

ELECTROCARDIOGRAM

Date ddmmmyy	Time 0-2400	NORMAL check	ABNORMAL check	Describe abnormalities
10Jul86				Sinus bradycardia with occasional junctional & low atrial rhythm
14Jul86	0725	✓		
19Jul86	1213	[illegible]	✓	nodal/low atrial rhythm
15Jul86	0828	[illegible]	✓	nodal & low atrial rhythm
16Jul86	0823	✓		
18Jul86	0828	[illegible]	✓	nodal & low atrial rhythm

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

ADVERSE EXPERIENCES

check if none occurred ☒ (Bgr)

#	ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
1	Increased LOH	18 Jul 96 dd mmm yy 0800 (0-2400)	dd mmm yy Unknown (0-2400)	☐ Mild ☒ Mod ☐ Sev	☐ DEF. ☐ PROB. ☒ POSS. ☐ DEF. NOT ☐ UNKNOWN	☒ None ☐ Treatment ☐ Stop test drug
#		dd mmm yy (0-2400)	dd mmm yy (0-2400)	☐ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☐ DEF. NOT ☐ UNKNOWN	☐ None ☐ Treatment ☐ Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	R L H F M L	02	PROTOCOL:DAMD 17-85-C-5133-03

OUTCOME
(To be completed for all subjects)

☒	Protocol completed	18~~Feb~~Jul16 ddmmmyy
☐	Premature termination of protocol	_____ ddmmmyy

REASON FOR PREMATURE TERMINATION
(Check appropriate category)

- ☐ Adverse Experience
- ☐ Died During Study
- ☐ Failure To Return For Follow-up
- ☐ Did Not Cooperate
- ☐ Protocol Violation
- ☐ Entry Violation
- ☐ Intercurrent Illness
- ☐ Administrative/Other

If terminated early, explain briefly:

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	R L H F M L	02	PROTOCOL: DAMD 17-85-C-5133 03

CONCOMITANT MEDICATIONS

DRUG NAME	TOTAL DAILY DOSE	DATE STARTED	DATE STOPPED
heparin flush	10cc - 100cc units	14 Jul 86	17 JUL 86

COMMENTS
(please date and sign all comments)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W -- F F M L	03	PROTOCOL:DAMD 17-85-C-5133-03

PROTOCOL

Study Day	Date ddmmmyy	Procedures
	08Jul86	Screening laboratory
	10Jul86	History, Physical Exam
0	19Jul86	Admission
3	21Jul86	Drug Administration

I certify that:

1) I have carefully examined all entries on the data collection forms, consisting of 14 pages, for subject #03.

2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Bruce G. Lietman M.D. 16, Dec, 86

Investigator's signature dd/mmm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W – F F M L	03	PROTOCOL:DAMD 17-85-C-5133-03

MEDICAL HISTORY

Date of evaluation 10/Jul/86 (dd mmm yy)

Examiner Brent G Petty MD

Dr. B.G. Petty (print name)

Date of birth 30/APR/55 (dd mmm yy)

Age 31 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		Asthma as child
Tobacco Use		✓	½ PPD
Alcohol Use		✓	1 beer/week
Recreational Drug Use	✓		
Medications past 2 weeks	✓		
Experimental Drug Exposure	✓		
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine(diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W F — M F L	03	PROTOCOL:DAMD 17-85-C-5133-03

PHYSICAL EXAMINATION
Date 10/Jul/86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
98.4F	80/min	14/min	110/52	188.0	94.0

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	mouth - 2 small 1-2mm macular red patches on hard palate
Chest, lungs		✓	few wheezes ® base on 2nd examination + barely clears c cough
Heart	✓		
Abdomen	✓		
Genitalia			Not Done
Rectal			Not Done
Extremities	✓		scars around knees + skin from skateboard hyperpigmented patch over ® 3rd MCP joint from remote trauma
Skin		✓	large scar ⓐ lower thorax from remote trauma, scar ® of umbilicus from dog bite, café au lait spot ~~LUQ~~ LUQ
Neurologic	✓		

CHEST X-RAY
Date 15/Jul/86

NORMAL	X	ABNORMAL		Describe abnormalities:

Examiner Brian G. Kelly (MD)
Dr. B.G. Kelly
print name

as of 07/28/86 YS

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	W — E F M L	03	PROTOCOL: DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0825	N.A	PO	

DOSAGE (total) 60 mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemo-~~ globin ~~%~~
	0	21Jul86	0757	0757	*	
	0.25	21Jul86	0840	0840	*	
	0.50	21Jul86	0855	0855	*	
	0.75	21Jul86	0910	0910	*	
	1.0	21Jul86	0925	0925	7.47	
	1.25	21Jul86	0940	0940	13.0	
	1.50	21Jul86	0955	0955	14.7	
	2.0	21Jul86	1025	1025	28.9	
	2.5	21Jul86	1055	1055	46.8	
	3.0	21Jul86	1125	1125	52.5	
	3.5	21Jul86	1155	1155	36.6	
	4.0	21Jul86	1225	1225	48.3	
	5.0	21Jul86	1325	1325	46.6	
	6.0	21Jul86	1425	1425	39.2	
	8.0	21Jul86	1625	1625	33.6	
	10.0	21Jul86	1825	1826	36.2	
	12.0	21Jul86	2025	2026	26.9	

7/28/86 JB

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W = F F M L	03	PROTOCOL:DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0825	N.A.	PO	

DOSAGE (total) 60 mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemoglobin~~ %
	24.0	22Jul86	0825	0825	15.0	
	36.0	22Jul86	2025	2027	12.0	
	48.0	23Jul86	0825	0835	*	
	60.0	23Jul86	2025	2147	*	
	72.0	24Jul86	0825	0828	*	
	84.0	24Jul86	2025	2032	*	
	96.0	25Jul86	0825	0835	*	

7-28-86 SB

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W - F F M L	03	PROTOCOL:DAMD 17-85-C-5133-03

URINE CONCENTRATIONS

STUDY:WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0825	NA	PO	

DOSAGE (total) 60mg

URINE CONCENTRATIONS

Sample No.	Scheduled Collection Time (hours)	Start Collection		End Collection		Total Volume (ml)	[WR6026] mg.
		ddmmmyy	0-2400	ddmmmyy	0-2400		
U01	-24 TO -12	20Jul86	0800	20Jul86	2005	1270	—
U02	-12 TO 0	20Jul86	2005	21Jul86	0800	1045	0
U03	0 TO 12	21Jul86	0800	21Jul86	2000	1390	0.170917
U04	12 TO 24	21Jul86	2000	22Jul86	0800	1855	0.109445
U05	24 TO 36	22Jul86	0800	22Jul86	2000	1328	0.065072
U06	36 TO 48	22Jul86	2000	23Jul86	0805	3130	0.046855
U07	48 TO 60	23Jul86	0805	23Jul86	2100	1695	0.018645
U08	60 TO 72	23Jul86	2100	24Jul86	0835	1805	0.013635
U09	72 TO 84	24Jul86	0835	29Jul86	2000	1650	0.0231
U10	84 TO 96	24Jul86	2000	25Jul86	0800	1720	0

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W - F F M L	03	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Screen -	Predrug 1	Predrug 2	Postdrug 4	Postdrug 5	Day
	08Jul86 ddmmmyy	19Jul86 ddmmmyy	21Jul86 ddmmmyy	22Jul86 ddmmmyy	23Jul86 ddmmmyy	Date
NA:135-148 MEQ/L	142	140	142	143	142	
K:3.5-5.0 MEQ/L	4.9	4.6	3.7	4.3	4.6	
CL:96-109 MEQ/L	108	109	108	111	108	
CO2:24-30 MEQ/L	26	15	20	19	19	
SUN:12-25 MG/DL	20	15	15	14	15	
CREAT:0.4-1.5 MG/DL	1.2	0.7	1.0	0.9	0.9	
GLU:70-115 MG/DL	98	70	69	90	86	
T.BILI:0.3-1.2MG/DL	0.5	0.2	0.6	0.6	0.5	
D.BILI:0.1-0.4MG/DL	0.1	0.1	0.1	0.1	0.0	
CA:9.0-11.0 MG/DL	10.0	9.6	9.5	9.7	9.9	
PO4:3.0-4.5 MG/DL	3.7	3.6	2.8	3.5	3.5	
URIC A:4.2-8.8MG/DL	9.4	7.4	6.5	7.5	7.4	
T. PROT:6.0-8.5G/DL	7.8	7.1	6.7	7.2	7.5	
ALB.:3.2-5.3 G/DL	4.8	4.4	4.2	N.D.	4.7	
AST:0-35 IU/L	20	14	23	23	27	
ALT:0-30 IU/L	7	7	10	10	16	
ALK PHOS:0-95 IU/L	53	45	48	46	49	
CHOL:151-268 MG/DL	190	177	184	183	197	
LDH:0-200 IU/L	151	161	147	190	170	
CPK:0-160 U/L(male)	285	338	213	200	187	
TG:20-190 MG/DL	164	~~62~~ 73	62	62	87	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W F - M F L	03	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Postdrug 7 25JuL86 ddmmmyy	follow-up 08Aug86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
					Day
					Date
NA:135-148 MEQ/L	141	ND			
K:3.5-5.0 MEQ/L	3.8	ND			
CL:96-109 MEQ/L	106	ND			
CO2:24-30 MEQ/L	22	ND			
SUN:12-25 MG/DL	15	10			
CREAT:0.4-1.5 MG/DL	1.0	1.1			
GLU:70-115 MG/DL	76	70			
T.BILI:0.3-1.2MG/DL	0.7	0.3			
D.BILI:0.1-0.4MG/DL	N.D.	0.1			
CA:9.0-11.0 MG/DL	9.8	9.7			
PO4:3.0-4.5 MG/DL	3.1	3.2			
URIC A:4.2-8.8MG/DL	6.8	8.6			
T. PROT:6.0-8.5G/DL	7.7	ND			
ALB.:3.2-5.3 G/DL	4.8	4.3			
AST:0-35 IU/L	41	22			
ALT:0-30 IU/L	21	11			
ALK PHOS:0-95 IU/L	46	47			
CHOL:151-268 MG/DL	203	166			
LDH:0-200 IU/L	201	ND			
CPK:0-160 U/L(male)	193	ND			
TG:20-190 MG/DL	60	ND			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W – F F M L	03	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Screen –	Predrug 1	Predrug 3	Postdrug 4	Postdrug 5	Day
		08Jul86	19Jul86	21Jul86	22Jul86	23Jul86	Date
		ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
WBC	4500-11000	6200	6400	5700	5000	4400	
RBC	4.50-5.90	4.74	4.21	4.28	4.37	4.58	
Hgb	13.9-16.3	15.3	13.5	14.4	14.6	13.8	
PCV	41.0-53.0	44.9	40.1	41.8	42.6	44.2	
Plt	150-350	331	323	298	330	309	
Bands	2-6%	3	7	3	2	1	
Polys	31-76%	38	38	35	48	33	
Eos	1-4%	5	3	3	1	2	
Bas		0	0	2	1	0	
Lymphs	24-44%	45	46	47	43	53	
Atyp Lym		2	0	1	0	0	
Monos	2-11%	7	6	9	5	11	
Other		0	0	0	6	6	
Methem:		15Jul86 0.1		0.1/0.0	0.1	0.4	
G-6-PD	7.4-9.4	7.0					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W -- F F M L	03	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

		Postdrug 7					Day
TEST	NORMAL	25Jul86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	Date
WBC	4500-11000	7300					
RBC	4.50-5.90	4.57					
Hgb	13.9-16.3	14.9					
PCV	41.0-53.0	43.3					
Plt	150-350	304					
Bands	2-6%	4					
Polys	31-76%	50					
Eos	1-4%	2					
Bas		1					
Lymphs	24-44%	33					
Atyp Lym		1					
Monos	2-11%	9					
Other		0					
methem.	0.0 - 1.5	0.3					
G-6-PD	7.4-9.4						

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	W — F F M L	03	PROTOCOL:DAMD 17-85-C-5133-03

URINALYSIS VALUES

Laboratory: JOHNS HOPKINS HOSPITAL

		Screen –	Predrug 1	4	Postdrug 5	7
		15Jul86 ddmmmyy	19Jul86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	25Jul86 ddmmmyy
Sp.Gr.		1.022	1.020			1.018
pH		6.0	6.0			6.0
Protein		Neg	Neg			Neg
Glucose		Neg	Neg			Neg
Ketones		Neg	Neg			Neg
Bili.		Neg	Neg			Neg
Occ.Bld.		Neg	Neg			Neg
Cast/lpf		0	ND			0
WBC/hpf		0				0
RBC/hpf		0				0
Epi./hpf		0-1				0
Crys/hpf		0				0
Bact/hpf		0				0

ELECTROCARDIOGRAM

Date ddmmmyy	Time 0-2400	NORMAL check	ABNORMAL check	Describe abnormalities
21Jul86	0705	✓		
21Jul86	1145	✓		
22Jul86	0912	✓		
23Jul86	0954	✓		
25Jul86	0850	✓		
15Jul86	1401	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	W F — M — E L	03	PROTOCOL:DAMD 17-85-C-5133-03

ADVERSE EXPERIENCES

check if none occurred ☐

#	ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
1	Mild elevation of AST	25 Jul 86 dd mmm yy _____ (0-2400)	08 Aug 86 dd mmm yy _____ (0-2400)	☒ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☒ DEF. NOT ☐ UNKNOWN	☒ None ☐ Treatment ☐ Stop test drug
#		___ ___ ___ dd mmm yy _____ (0-2400)	___ ___ ___ dd mmm yy _____ (0-2400)	☐ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☐ DEF. NOT ☐ UNKNOWN	☐ None ☐ Treatment ☐ Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	W — E F M L	03	PROTOCOL:DAMD 17-85-C-5133-03

OUTCOME
(To be completed for all subjects)

☒	Protocol completed	15Jul86 ddmmmyy
☐	Premature termination of protocol	_____ ddmmmyy

REASON FOR PREMATURE TERMINATION
(Check appropriate category)

- ☐ Adverse Experience
- ☐ Died During Study
- ☐ Failure To Return For Follow-up
- ☐ Did Not Cooperate
- ☐ Protocol Violation
- ☐ Entry Violation
- ☐ Intercurrent Illness
- ☐ Administrative/Other

If terminated early, explain briefly:

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	W F — M F L	03	PROTOCOL: DAMD 17-85-C-5133 03

CONCOMITANT MEDICATIONS

DRUG NAME	TOTAL DAILY DOSE	DATE STARTED	DATE STOPPED
heparin flush	100-1000 unit	2 Jul 86	

COMMENTS
(please date and sign all comments)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

PROTOCOL

Study Day	Date ddmmmyy	Procedures
	14Jul86	Screening laboratory
	15Jul86	History, Physical Exam
0	19Jul86	Admission
3	21Jul86	Drug Administration

I certify that:

1) I have carefully examined all entries on the data collection forms, consisting of 14 pages, for subject # 04.

2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent Lietman M.D. — 16/Dec/86

Investigator's signature — dd/mmm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

MEDICAL HISTORY

Date of evaluation 08/Jul/86 (dd mmm yy)

Examiner Brent G. Petty MD
Dr. B.G. Petty
print name

Date of birth 17/MAY/62 (dd mmm yy)

Age 24 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	½ PPD
Alcohol Use		✓	1 beer/day
Recreational Drug Use		✓	Joint/d, last 2-D ago
Medications past 2 weeks		✓	? Darvon ~ 2D ago
Experimental Drug Exposure		✓	tobramycin study
Blood or plasma donor	✓		
Prior Surgery		✓	umbilical surgery age 10
Eye, ear, nose, throat	✓		
Endocrine(diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	GC in 1981, resolved c PCN
Musculoskeletal	✓		
Neuropsychiatric	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

PHYSICAL EXAMINATION
Date 15/Jul/86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
36.4 C	68/min	12/min	118/62	165.0	54.5

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓	✓B	Shotty nodes both ant. cervical areas
EENT		✓	Ears - Sclerotic TM's R>L
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			Not Done
Rectal			Not Done
Extremities	✓		
Skin		✓	Scar (L) wrist from surgery 11/85 Tinea versicolor on back L>R
Neurologic	✓		

CHEST X-RAY
Date 15/Jul/86

NORMAL	Y	ABNORMAL		Describe abnormalities:

Examiner [signature]
Dr. B G Petty
print name

7/28/86 gb

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0810	NA	PO	

DOSAGE (total) 60mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemoglobin~~ *
	0	21Jul86	0800	0800	*	
	0.25	21Jul86	0825	0825	*	
	0.50	21Jul86	0840	0840	12.9	
	0.75	21Jul86	0855	0855	18.0	
	1.0	21Jul86	0910	0910	37.8	
	1.25	21Jul86	0925	0925	51.2	
	1.50	21Jul86	0940	0940	59.6	
	2.0	21Jul86	1010	1010	82.6	
	2.5	21Jul86	1040	1040	85.6	
	3.0	21Jul86	1110	1110	68.6	
	3.5	21Jul86	1140	1140	68.3	
	4.0	21Jul86	1210	1210	62.8	
	5.0	21Jul86	1310	1310	75.5	
	6.0	21Jul86	1410	1410	52.4	
	8.0	21Jul86	1610	1613	36.8	
	10.0	21Jul86	1810	1810	37.2	
	12.0	21Jul86	2010	2010	24.1	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0810	N.A.	PO	

* Below Assay Sensitivity

DOSAGE (total) 60 mg

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemoglobin~~ *
	24.0	22Jul86	0810	0810	8.79	
	36.0	22Jul86	2010	2010	*	
	48.0	23Jul86	0810	0810	*	
	60.0	23Jul86	2010	2137	*	
	72.0	24Jul86	0810	0812	*	
	84.0	24Jul86	2010	2015	*	
	96.0	25Jul86	0810	0810	*	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

URINE CONCENTRATIONS

STUDY:WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0810	N.A.	PO	

DOSAGE (total) 60mg

URINE CONCENTRATIONS

Sample No.	Scheduled Collection Time (hours)	Start Collection		End Collection		Total Volume (ml)	[WR6026] mg.
		ddmmmyy	0-2400	ddmmmyy	0-2400		
U01	-24 TO -12	20Jul86	0800	20Jul86	2000	755	———
U02	-12 TO 0	20Jul86	2000	21Jul86	0800	735	0
U03	0 TO 12	21Jul86	0800	21Jul86	2000	510	0.107920
U04	12 TO 24	21Jul86	2000	22Jul86	0800	595	0.077053
U05	24 TO 36	22Jul86	0800	22Jul86	2000	432	0.021987
U06	36 TO 48	22Jul86	2000	23Jul86	0800	745	0.011287
U07	48 TO 60	23Jul86	0800	23Jul86	2000	685	0.013104
U08	60 TO 72	23Jul86	2000	24Jul86	0810	490	0.008106
U09	72 TO 84	24Jul86	0810	24Jul86	2000	1050	0.010592
U10	84 TO 96	24Jul86	2000	25Jul86	0800	745	0

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Screen -	Predrug 1	Predrug 2	Postdrug 4	Postdrug 5	Day
	14Jul86 ddmmmyy	19Jul86 ddmmmyy	21Jul86 ddmmmyy	22Jul86 ddmmmyy	23Jul86 ddmmmyy	Date
NA:135-148 MEQ/L	140	144	142	138	139	
K:3.5-5.0 MEQ/L	4.5	4.3	4.4	5.0	4.2	
CL:96-109 MEQ/L	106	104	106	107	108	
CO2:24-30 MEQ/L	28	24	28	20	20	
SUN:12-25 MG/DL	12	12	9	10	13	
CREAT:0.4-1.5 MG/DL	0.7	1.0	1.0	1.0	0.9	
GLU:70-115 MG/DL	76	72	70	84	76	
T.BILI:0.3-1.2MG/DL	0.6	0.5	0.6	0.9	0.7	
D.BILI:0.1-0.4MG/DL	0.1	0.1	0.1	0.1	0.1	
CA:9.0-11.0 MG/DL	10.3	9.8	9.9	10.2	9.5	
PO4:3.0-4.5 MG/DL	4.7	5.2	3.7	3.5	3.8	
URIC A:4.2-8.8MG/DL	7.0	7.3	5.8	6.5	6.9	
T. PROT:6.0-8.5G/DL	7.4	7.6	7.4	6.9	6.7	
ALB.:3.2-5.3 G/DL	4.6	4.6	4.3	ND	4.3	
AST:0-35 IU/L	25	27	21	21	19	
ALT:0-30 IU/L	12	13	15	15	7	
ALK PHOS:0-95 IU/L	66	61	57	62	57	
CHOL:151-268 MG/DL	207	220	214	173	170	
LDH:0-200 IU/L	189	ND	168	ND	166	
CPK:0-160 U/L(male)	379	ND	278	169	169	
TG:20-190 MG/DL	50	~~92~~ 93	92	79	82	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Postdrug 7 Day 25Jul86 Date ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy
NA:135-148 MEQ/L	143				
K:3.5-5.0 MEQ/L	4.2				
CL:96-109 MEQ/L	105				
CO2:24-30 MEQ/L	25				
SUN:12-25 MG/DL	10				
CREAT:0.4-1.5 MG/DL	1.0				
GLU:70-115 MG/DL	72				
T.BILI:0.3-1.2MG/DL	0.8				
D.BILI:0.1-0.4MG/DL	0.1				
CA:9.0-11.0 MG/DL	9.5				
PO4:3.0-4.5 MG/DL	3.8				
URIC A:4.2-8.8MG/DL	7.1				
T. PROT:6.0-8.5G/DL	7.0				
ALB.:3.2-5.3 G/DL	N.D.				
AST:0-35 IU/L	18				
ALT:0-30 IU/L	14				
ALK PHOS:0-95 IU/L	60				
CHOL:151-268 MG/DL	181				
LDH:0-200 IU/L	146				
CPK:0-160 U/L(male)	186				
TG:20-190 MG/DL	89				

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Screen -	Predrug 1	Predrug 3	Postdrug 4	Postdrug 5	Day
		14Jul86	19Jul86	21Jul86	22Jul86	23Jul86	Date
		ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
WBC	4500-11000	7200	6700	6400	9500	8400	
RBC	4.50-5.90	4.73	4.87	4.70	4.49	4.61	
Hgb	13.9-16.3	14.6	14.6	14.8	14.5	14.0	
PCV	41.0-53.0	43.6	44.8	44.2	42.1	43.1	
Plt	150-350	308	341	295	271	260	
Bands	2-6%	4	1	0	3	5	
Polys	31-76%	52	54	64	69	64	
Eos	1-4%	3	1	0	1	0	
Bas		1	0	0	0	0	
Lymphs	24-44%	27	43	32	<1	<1	
Atyp Lym		0	0	0	0	0	
Monos	2-11%	13	1	4	6	7	
Other		0	0	0	0	0	
Methem.	0.0-1.5	15Jul86 0.0		0.0/0.1	0.0	0.3	
G-6-PD	7.4-9.4	8.3					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Postdrug 7 25Jul86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
						Day
						Date
WBC	4500-11000	6800				
RBC	4.50-5.90	4.66				
Hgb	13.9-16.3	14.1				
PCV	41.0-53.0	43.2				
Plt	150-350	279				
Bands	2-6%	2				
Polys	31-76%	51				
Eos	1-4%	1				
Bas		1				
Lymphs	24-44%	39				
Atyp Lym		0				
Monos	2-11%	6				
Other		0				
Methem.	0.0 - 1.5	0.0				
G-6-PD	7.4-9.4					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

URINALYSIS VALUES

Laboratory: JOHNS HOPKINS HOSPITAL

		Screen –	Predrug 1	4	Postdrug 5	7
		15Jul86 ddmmmyy	19Jul86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	25Jul86 ddmmmyy
Sp.Gr.		1.029	1.017			1.025
pH		6.0	6.5			6.5
Protein		Neg	Neg			Neg
Glucose		Neg	Neg			Neg
Ketones		Neg	Neg			Neg
Bili.		Neg	Neg			Neg
Occ.Bld.		Neg	Neg			Neg
Cast/lpf		0	ND			0
WBC/hpf		0				0
RBC/hpf		0				0
Epi./hpf		0				0
Crys/hpf		0				0
Bact/hpf		0				0

ELECTROCARDIOGRAM

Date ddmmmyy	Time 0-2400	NORMAL check	ABNORMAL check	Describe abnormalities
15Jul86			✓	Short PR interval, U waves
21Jul86	0650		✓	Short PR interval, U waves
21Jul86	1226		✓	No significant change
22Jul86	0855		✓	Minor T wave change in III, short PR
23Jul86	0857		✓	No significant change
25Jul86	0826		✓	Trace back to original appearance in III, short PR
15Jul86			✓	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

ADVERSE EXPERIENCES

check if none occurred ☒

ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#					
	__ __ __ dd mmm yy _____ (0-2400)	__ __ __ dd mmm yy _____ (0-2400)	☐ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☐ DEF. NOT ☐ UNKNOWN	☐ None ☐ Treatment ☐ Stop test drug
#					
	__ __ __ dd mmm yy _____ (0-2400)	__ __ __ dd mmm yy _____ (0-2400)	☐ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☐ DEF. NOT ☐ UNKNOWN	☐ None ☐ Treatment ☐ Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133-03

OUTCOME
(To be completed for all subjects)

☒	Protocol completed	25JUL86 ddmmmyy
☐	Premature termination of protocol	_____ ddmmmyy

REASON FOR PREMATURE TERMINATION
(Check appropriate category)

- ☐ Adverse Experience
- ☐ Died During Study
- ☐ Failure To Return For Follow-up
- ☐ Did Not Cooperate
- ☐ Protocol Violation
- ☐ Entry Violation
- ☐ Intercurrent Illness
- ☐ Administrative/Other

If terminated early, explain briefly:

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	L M H F M L	04	PROTOCOL:DAMD 17-85-C-5133 03

CONCOMITANT MEDICATIONS

DRUG NAME	TOTAL DAILY DOSE	DATE STARTED	DATE STOPPED
heparin	100-1000 units	21 Jul 86	24 Jul 86

COMMENTS
(please date and sign all comments)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	D L A F M L	05	PROTOCOL:DAMD 17-85-C-5133-03

PROTOCOL

Study Day	Date ddmmmyy	Procedures
	14Jul86	Screening laboratory
	15Jul86	History, Physical Exam
0	19Jul86	Admission
3	24Jul86	Drug Administration

I certify that:

1) I have carefully examined all entries on the data collection forms, consisting of __14__ pages, for subject #_05___.

2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Robert G. Lietman M.D. — Investigator's signature

16/Dec/86 — dd/mmm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	D L A F M L	05	PROTOCOL:DAMD 17-85-C-5133-03

MEDICAL HISTORY

Date of evaluation 15/Jul/86 (dd mmm yy)

Examiner Brent G Petty M.D.
Dr. B G. Petty
print name

Date of birth 29/Sep/58 (dd mmm yy)

Age 27 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	½ PPD
Alcohol Use	✓		Quit 4/86
Recreational Drug Use		✓	last 3/86 (MJ), occ drug use [illegible]
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	pyrids, ceftriaxone
Blood or plasma donor	✓		
Prior Surgery		✓	Umbilical hernia repair age 4
Eye, ear, nose, throat	✓		
Endocrine(diabetes,thyroid)	✓		
C-V (heart murmur,HBP)	✓		
Pulmonary (cough,asthma)	✓		
Hepatitis,gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	D L A F M L	05	PROTOCOL: DAMD 17-85-C-5133-03

PHYSICAL EXAMINATION

Date 05/Jul/86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
36.7 C	72/min	10/min	108/64	195.0	105.0

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		1x0.5cm node Ⓡ neck, unchanged x years [illegible]
EENT		✓	ears ceruminous, bilat
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			ND
Rectal			ND
Extremities	✓		
Skin		✓	scars Ⓛ heels, upper back, umbilicus
Neurologic	✓		

CHEST X-RAY

Date 15/Jan/86

NORMAL	X	ABNORMAL		Describe abnormalities:

Examiner [signature]

Dr. B.G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	D L A (F M L)	05	PROTOCOL: DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0805	N.A.	PO	

DOSAGE (total) 60 mg

*Below Assay Sensitivity

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemoglobin~~ *
	0	21Jul86	0755	0755	*	
	0.25	21Jul86	0820	0820	*	
	0.50	21Jul86	0835	0835	*	
	0.75	21Jul86	0850	0850	*	
	1.0	21Jul86	0905	0905	*	
	1.25	21Jul86	0920	0920	10.6	
	1.50	21Jul86	0935	0935	19.4	
	2.0	21Jul86	1005	1005	24.9	
	2.5	21Jul86	1035	1035	23.2	
	3.0	21Jul86	1105	1107	48.9	
	3.5	21Jul86	1135	1135	53.3	
	4.0	21Jul86	1205	1205	63.4	
	5.0	21Jul86	1305	1305	72.0	
	6.0	21Jul86	1405	1405	60.1	
	8.0	21Jul86	1605	1608	47.2	
	10.0	21Jul86	1805	1806	38.3	
	12.0	21Jul86	2005	2005	32.7	

7-28-86 93

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	D L A F M L	05	PROTOCOL: DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0805	N.A.	PO	

DOSAGE (total) 60 mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemoglobin~~ *
	24.0	22Jul86 D	0805	0805	12.0	
	36.0	22Jul86	2005	2005	7.67	
	48.0	23Jul86	0805	0805	*	
	60.0	23Jul86	~~0805~~ 2005	2142	*	
	72.0	24 Jul86	0805	0810	*	
	84.0	24 Jul86	2005	2032	*	
	96.0	25Jul86	0805	0805	*	

7.28.86 B3

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	D L A F M L	05	PROTOCOL:DAMD 17-85-C-5133-03

URINE CONCENTRATIONS

STUDY:WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0805	0805	PO	

DOSAGE (total) 60 mg

URINE CONCENTRATIONS

Sample No.	Scheduled Collection Time (hours)	Start Collection		End Collection		Total Volume (ml)	[WR6026] mcg.
		ddmmmyy	0-2400	ddmmmyy	0-2400		
U01	-24 TO -12	20Jul86	0800	20Jul86	2000	1790	—
U02	-12 TO 0	20Jul86	2000	21Jul86	0800	815	0
U03	0 TO 12	21Jul86	0800	21Jul86	2000	485	0.036373
U04	12 TO 24	21Jul86	2000	22Jul86	0800	1050	0.061078
U05	24 TO 36	22Jul86	0800	22Jul86	2000	802	0.021777
U06	36 TO 48	22Jul86	2000	23Jul86	0800	1160	0.014318
U07	48 TO 60	23Jul86	0800	23Jul86	2000	1000	0.006443
U08	60 TO 72	23Jul86	2000	24Jul86	0800	1070	0.003892
U09	72 TO 84	24Jul86	0800	24Jul86	2000	750	0.003612
U10	84 TO 96	24Jul86	2000	25Jul86	0800	1025	0.002577

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	D L A F M L	05	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Screen -	Predrug 1	Predrug 2	Postdrug 4	Postdrug 5	Day
	14Jul86	19Jul86	21Jul86	22Jul86	23Jul86	Date
	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
NA:135-148 MEQ/L	143	139	138	137	138	
K:3.5-5.0 MEQ/L	4.6	4.6	4.0	3.9	4.4	
CL:96-109 MEQ/L	105	103	101	104	106	
CO2:24-30 MEQ/L	24	20	24	21	21	
SUN:12-25 MG/DL	13	11	10	13	15	
CREAT:0.4-1.5 MG/DL	1.1	1.1	0.9	1.1	1.0	
GLU:70-115 MG/DL	103	81	86	92	89	
T.BILI:0.3-1.2MG/DL	0.3	0.2	0.5	0.4	0.4	
D.BILI:0.1-0.4MG/DL	0.1	0.1	0.1	0.1	0.1	
CA:9.0-11.0 MG/DL	not done	9.7	9.2	9.3	9.4	
PO4:3.0-4.5 MG/DL	3.7	3.4	3.6	3.3	4.1	
URIC A:4.2-8.8MG/DL	4.9	4.9	5.4	5.7	6.2	
T. PROT:6.0-8.5G/DL	7.6	7.4	6.8	6.9	7.1	
ALB. :3.2-5.3 G/DL	4.6	4.4	4.1	4.2	4.3	
AST:0-35 IU/L	28	28	30	27	N.D.	
ALT:0-30 IU/L	25	33	39	36	40	
ALK PHOS:0-95 IU/L	56	55	49	59	51	
CHOL:151-268 MG/DL	179	193	172	162	174	
LDH:0-200 IU/L	153	154	133	143	203	
CPK:0-160 U/L(male)	210	271	159	142	140	
TG:20-190 MG/DL	224	ND	157	139	147	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	D L A F M L	05	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Postdrug 7	follow-up (#)			Day
	25Jul86	05Aug86	_____	_____	_____	Date
	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
NA:135-148 MEQ/L	137	ND			
K:3.5-5.0 MEQ/L	4.1	ND			
CL:96-109 MEQ/L	104	ND			
CO2:24-30 MEQ/L	21	ND			
SUN:12-25 MG/DL	13	10			
CREAT:0.4-1.5 MG/DL	1.1	1.1			
GLU:70-115 MG/DL	87	108			
T.BILI:0.3-1.2MG/DL	0.4	0.5			
D.BILI:0.1-0.4MG/DL	0.1	0.1			
CA:9.0-11.0 MG/DL	10.2	10.0			
PO4:3.0-4.5 MG/DL	4.0	3.2			
URIC A:4.2-8.8MG/DL	6.6	Channel malf.			
T. PROT:6.0-8.5G/DL	7.8	7.8			
ALB.:3.2-5.3 G/DL	4.4	4.6			
AST:0-35 IU/L	29	16			
ALT:0-30 IU/L	44	19			
ALK PHOS:0-95 IU/L	54	41			
CHOL:151-268 MG/DL	191	175			
LDH:0-200 IU/L	166	141			
CPK:0-160 U/L(male)	169	ND			
TG:20-190 MG/DL	160	ND			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	D L A F M L	05	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Screen -	Predrug 1	Predrug 3	Postdrug 4	Postdrug 5	Day
		14Jul86	19Jul86	21Jul86	22Jul86	23Jul86	Date
		ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
WBC	4500-11000	4700	6100	6300	7500	8600	
RBC	4.50-5.90	5.11	5.00	4.73	4.77	4.96	
Hgb	13.9-16.3	14.8	13.8	13.9	14.1	13.9	
PCV	41.0-53.0	43.8	42.4	40.9	41.4	42.6	
Plt	150-350	207	232	233	283	267	
Bands	2-6%	2	2	2	4	4	
Polys	31-76%	29	40	52	46	45	
Eos	1-4%	2	1	1	2	1	
Bas		0	0	0	0	0	
Lymphs	24-44%	55	50	37	40	44	
Atyp Lym		0	0	1	0	1	
Monos	2-11%	13	7	7	8	4	
Other						1 met	
Methem:		1.4		0.0 / 0.0	0.0	0.2	
G-6-PD	7.4-9.4	7.8					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	D L A F M L	05	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Postdrug 7 25Jul86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
						Day
						Date
WBC	4500-11000	7800				
RBC	4.50-5.90	4.97				
Hgb	13.9-16.3	14.2				
PCV	41.0-53.0	42.5				
Plt	150-350	286				
Bands	2-6%	3				
Polys	31-76%	36				
Eos	1-4%	1				
Bas		0				
Lymphs	24-44%	54				
Atyp Lym		0				
Monos	2-11%	6				
Other		0				
methem.	0.0 - 1.5	0.7				
G-6-PD	7.4-9.4					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	D L A F M L	05	PROTOCOL: DAMD 17-85-C-5133-03

URINALYSIS VALUES

Laboratory: JOHNS HOPKINS HOSPITAL

		Screen -	Predrug 1	4	Postdrug 5	7
		15Jul86 ddmmmyy	19Jul86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	25Jul86 ddmmmyy
Sp. Gr.		1.026	1.024			1.027
pH		6.5	6.0			6.0
Protein		Neg	Neg			Neg
Glucose		Neg	Neg			Neg
Ketones		Neg	Neg			Neg
Bili.		Neg	Neg			Neg
Occ. Bld.		Neg	Neg			Neg
Cast/lpf		0	1			0
WBC/hpf		0				0-1/hpf rare
RBC/hpf		0				0
Epi./hpf		0				0
Crys/hpf		0				0
Bact/hpf		0				0

ELECTROCARDIOGRAM

Date ddmmmyy	Time 0-2400	NORMAL check	ABNORMAL check	Describe abnormalities
15Jul86	1527		✓	
21Jul86	0659		✓	(IRBBB) incomplete right bundle branch block/IRVH
21Jul86	1237		✓	IRBBB
22Jul86	0905		✓	IRBBB
23Jul86	1000		✓	IRBBB
25Jul86	0817		✓	IRBBB

Screen

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	D L A F M L	05	PROTOCOL:DAMD 17-85-C-5133-03

ADVERSE EXPERIENCES

check if none occurred ☐

#	ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
1	Nausea started AL BJP	19 Jul 96 dd mmm yy _____ (0-2400)	(BJP) 05 Aug 96 dd mmm yy _____ (0-2400)	☒ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☒ DEF. NOT ☐ UNKNOWN	☒ None ☐ Treatment ☐ Stop test drug
1	Nausea started CJP	23 Jul 96 dd mmm yy _____ (0-2400)	(BJP) 25 Jul 96 dd mmm yy _____ (0-2400)	☒ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☒ DEF. NOT ☐ UNKNOWN	☒ None ☐ Treatment ☐ Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	D L A F M L	05	PROTOCOL:DAMD 17-85-C-5133-03

OUTCOME
(To be completed for all subjects)

☒	Protocol completed	25 Jul 86 ddmmmyy
☐	Premature termination of protocol	_____ ddmmmyy

REASON FOR PREMATURE TERMINATION
(Check appropriate category)

- ☐ Adverse Experience
- ☐ Died During Study
- ☐ Failure To Return For Follow-up
- ☐ Did Not Cooperate
- ☐ Protocol Violation
- ☐ Entry Violation
- ☐ Intercurrent Illness
- ☐ Administrative/Other

If terminated early, explain briefly:

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	D L A F M L	05	PROTOCOL: DAMD 17-85-C-5133 03

CONCOMITANT MEDICATIONS

DRUG NAME	TOTAL DAILY DOSE	DATE STARTED	DATE STOPPED
heparin solution	100-1000 units	21 Jul 86	24 Jul 86

COMMENTS
(please date and sign all comments)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M — P F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

PROTOCOL

Study Day	Date ddmmmyy	Procedures
	22Jul86	Screening laboratory
	13Aug86	History, Physical Exam
0	16Aug86	Admission
3	18Aug86	Drug Administration

I certify that:

1) I have carefully examined all entries on the data collection forms, consisting of 14 pages, for subject # 06.

2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent T. Lietman M.D. 16/Dec/86
Investigator's signature dd/mmm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M -- P F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

MEDICAL HISTORY

Date of evaluation 13/Aug/86 (dd mmm yy)

Examiner [signature]
Dr. B. G. Petty
print name

Date of birth 16/Mar/66 (dd mmm yy)

Age 20 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	½ PPD
Alcohol Use	✓		
Recreational Drug Use		✓	MJ ø weekend
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	ceftriaxone, pyridostigmine
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine(diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M — P F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

PHYSICAL EXAMINATION
Date 31/Aug/86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
36.7 C	070/min	16/min	110/70	176.0	70.5

GENERAL EXAMINATION: (check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓	~~✓~~	
ENT		✓	minimal arteriolar narrowing Slight wide + deep optic ~~Be~~ cups
Chest, lungs	✓		Mild rhinchus sounds ℮ expiration
Heart	✓		
Abdomen	✓		
Genitalia	not done		
Rectal	not done		
Extremities	✓		
Skin		✓	Burn scars ① upper arm, wound scar ℮ thumb
Neurologic	✓		

CHEST X-RAY
Date 02/Feb/86

NORMAL	X	ABNORMAL		Describe abnormalities:

Examiner Brent G. Petty, M.D.

Dr. B. G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M — P F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	18 Aug 86	0800	N.A.	PO	

* Below Assay Sensitivity

DOSAGE (total) 60 mg

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemo-globin~~ *
	0	18 Aug 86	0755	0755	*	
	0.25	18 Aug 86	0815	0815	*	
	0.50	18 Aug 86	0830	0830	8.58	
	0.75	18 Aug 86	0845	0845	13.7	
	1.0	18 Aug 86	0900	0900	24.0	
	1.25	18 Aug 86	0915	0915	29.4	
	1.50	18 Aug 86	0930	0930	31.6	
	2.0	18 Aug 86	1000	1000	49.0	
	2.5	18 Aug 86	1030	1030	42.9	
	3.0	18 Aug 86	1100	1100	60.3	
	3.5	18 Aug 86	1130	1130	54.5	
	4.0	18 Aug 86	1200	1200	60.4	
	5.0	18 Aug 86	1300	1300	50.5	
	6.0	18 Aug 86	1400	1400	50.2	
	8.0	18 Aug 86	1600	1600	38.5	
	10.0	18 Aug 86	1800	1800	32.6	
	12.0	18 Aug 86	2000	2000	30.2	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M__P__ F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	18 Aug 86	0800	N.A.	PO	

DOSAGE (total) 60 mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemo-globin~~ %
	24.0	19 Aug 86	0800	0805	13.4	
	36.0	19 Aug 86	2000	2000	10.4	
	48.0	20 Aug 86	0800	0800	7.73	
	60.0	20 Aug 86	2000	2003	*	
	72.0	21 Aug 86	0800	0802	*	
	84.0	21 Aug 86	2000	2000	*	
	96.0	22 Aug 86	0800	0800	*	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	M — P F M L	06	PROTOCOL: DAMD 17-85-C-5133-03

URINE CONCENTRATIONS

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	18 Aug 86	0800	N.A.	PO	

DOSAGE (total) 60mg

URINE CONCENTRATIONS

Sample No.	Scheduled Collection Time (hours)	Start Collection		End Collection		Total Volume (ml)	[WR6026] mg.
		ddmmmyy	0-2400	ddmmmyy	0-2400		
U01	-24 TO -12	17 Aug 86	0800	17 Aug 86	2000	2000	—
U02	-12 TO 0	17 Aug 86	2000	18 Aug 86	~~0800~~ 0758 SS	1550	0
U03	0 TO 12	18 Aug 86	~~0800~~ 0758 SS	18 Aug 86	2000	1230	0.12177
U04	12 TO 24	18 Aug 86	2000	19 Aug 86	0800	1345	0.11836
U05	24 TO 36	19 Aug 86	0800	19 Aug 86	2000	1960	0.05292
U06	36 TO 48	19 Aug 86	2000	20 Aug 86	0800	1480	0.04144
U07	48 TO 60	20 Aug 86	0800	20 Aug 86	2000	950	0.0133
U08	60 TO 72	20 Aug 86	2000	21 Aug 86	~~0800~~ 0758 SS	1635	0.031065
U09	72 TO 84	21 Aug 86	~~0800~~ 0756 SS	21 Aug 86	2000	1600	0
U10	84 TO 96	21 Aug 86	2000	22 Aug 86	0800	1570	0

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M — P F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Screen -	Predrug 1	Predrug 23	Postdrug 4	Postdrug 5	Day
	22Jul86 ddmmmyy	16Aug86 ddmmmyy	18Aug86 ddmmmyy	19Aug86 ddmmmyy	20Aug86 ddmmmyy	Date
NA:135-148 MEQ/L	140	142	141	140	140	
K:3.5-5.0 MEQ/L	4.3	4.1	4.4	4.1	4.2	
CL:96-109 MEQ/L	109	107	108	106	105	
CO2:24-30 MEQ/L	20	17	18	23	25	
SUN:12-25 MG/DL	13	8	7	7	13	
CREAT:0.4-1.5 MG/DL	1.3	1.0	1.1	1.1	1.0	
GLU:70-115 MG/DL	129	60	80	79	75	
T.BILI:0.3-1.2MG/DL	1.1	0.3	0.5	0.4	0.4	
D.BILI:0.1-0.4MG/DL	0.1	0.1	0.0	0.0	0.0	
CA:9.0-11.0 MG/DL	10.6	9.2	9.3	9.5	9.7	
PO4:3.0-4.5 MG/DL	3.8	4.1	ND	4.7	5.2	
URIC A:4.2-8.8MG/DL	4.9	4.5	4.2	ND	4.0	
T. PROT:6.0-8.5G/DL	7.6	6.1	6.2	6.1	6.4	
ALB.:3.2-5.3 G/DL	4.7	4.0	4.0	4.1	4.3	
AST:0-35 IU/L	27	21	18	22	22	
ALT:0-30 IU/L	18	15	14	19	21	
ALK PHOS:0-95 IU/L	43	42	43	43	48	
CHOL:151-268 MG/DL	149	147	164	154	165	
LDH:0-200 IU/L	142	134	146	123	115	
CPK:0-160 U/L(male)	348	163	111	102	116	
TG:20-190 MG/DL	44	45	86	92	255	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M ~ P F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Postdrug 7 Day 22Aug86 Date ddmmmyy	23Sept.86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
NA:135-148 MEQ/L	139	ND			
K:3.5-5.0 MEQ/L	4.1				
CL:96-109 MEQ/L	103				
CO2:24-30 MEQ/L	27				
SUN:12-25 MG/DL	13				
CREAT:0.4-1.5 MG/DL	1.0				
GLU:70-115 MG/DL	69				
T.BILI:0.3-1.2MG/DL	0.4				
D.BILI:0.1-0.4MG/DL	0.0				
CA:9.0-11.0 MG/DL	9.4				
PO4:3.0-4.5 MG/DL	Channel Malf.				
URIC A:4.2-8.8MG/DL	4.0				
T. PROT:6.0-8.5G/DL	7.0				
ALB.:3.2-5.3 G/DL	4.7				
AST:0-35 IU/L	53	34			
ALT:0-30 IU/L	49	[illegible]10			
ALK PHOS:0-95 IU/L	46	[illegible]			
CHOL:151-268 MG/DL	182	ND			
LDH:0-200 IU/L	148				
CPK:0-160 U/L(male)	140				
TG:20-190 MG/DL	218				

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M = P F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Screen -	Predrug 1	Predrug 3	Postdrug 4	Postdrug 5	Day
		22Jul86	16Aug86	18Aug86	19Aug86	20Aug86	Date
		ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
WBC	4500-11000	6900	10300	7300	7000	8100	
RBC	4.50-5.90	5.31	4.71	5.14	5.01	5.10	
Hgb	13.9-16.3	15.2	13.6	15.4	14.7	15.4	
PCV	41.0-53.0	45.8	40.8	45.2	43	44.0	
Plt	150-350	268	266	265	286	272	
Bands	2-6%	1	2	0	0	0	
Polys	31-76%	51	61	58	61	56	
Eos	1-4%	1	1	0	4	2	
Bas		0	0	1	0	0	
Lymphs	24-44%	40	31	37	33	32	
Atyp Lym		1	0	0	0	1	
Monos	2-11%	6	5	4	2	9	
Other		0	0	0	0	0	
Methem:		0.5		0.2	0.3	0.7	
G-6-PD	7.4-9.4	9.8					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M = L F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Postdrug 7 22Aug86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
		Day				
		Date				
WBC	4500-11000	9600				
RBC	4.50-5.90	5.21				
Hgb	13.9-16.3	16.1				
PCV	41.0-53.0	45.7				
Plt	150-350	274				
Bands	2-6%	1				
Polys	31-76%	63				
Eos	1-4%	3				
Bas		1				
Lymphs	24-44%	29				
Atyp Lym		1				
Monos	2-11%	2				
Other		0				
mothem.		0.7				
G-6-PD	7.4-9.4					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	M -- P F M L	06	PROTOCOL: DAMD 17-85-C-5133-03

URINALYSIS VALUES

Laboratory: JOHNS HOPKINS HOSPITAL

		Screen -	Predrug 1	4	Postdrug 5	7
		13Aug86 ddmmmyy	16Aug86 ddmmmyy	~~8~~ ddmmmyy	_____ ddmmmyy	22Aug86 ddmmmyy
Sp.Gr.		1.017	1.022			1,016
pH		7.0	6.5			6.0
Protein		Neg	Neg			neg
Glucose		Neg	Neg			neg
Ketones		Neg	Neg			neg
Bili.		Neg	Neg			neg
Occ.Bld.		Neg	neg			neg
Cast/lpf		0	0			0
WBC/hpf		rare	rare			0
RBC/hpf		rare	0			0
Epi./hpf		0	0			2-4
Crys/hpf		0	0			0
Bact/hpf		0	0			0

ELECTROCARDIOGRAM

Date ddmmmyy	Time 0-2400	NORMAL check	ABNORMAL check	Describe abnormalities
13Aug86 18Aug86	0745	✓ ✓		
18 Aug 86	1147		✓	nodal or low atrial rhythm
19 Aug 86	0830	✓		
20 Aug 86	0825	✓		
22 Aug 86	0810	✓		

Screen

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	M -- P F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

ADVERSE EXPERIENCES

check if none occurred ☐

#	ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
1	Increase in triglycerides	20 Aug 82 dd mmm yy 0800 (0-2400)	___ ___ ___ dd mmm yy Unknown ___ (0-2400)	☒ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☒ POSS. ☐ DEF. NOT ☐ UNKNOWN	☒ None ☐ Treatment ☐ Stop test drug
2	Increase in serum transferase	22 Aug 82 dd mmm yy 0800 (0-2400)	23 Sep 82 dd mmm yy 1030 (0-2400)	☒ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☒ POSS. ☐ DEF. NOT ☐ UNKNOWN	☒ None ☐ Treatment ☐ Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	M L F M L	06	PROTOCOL:DAMD 17-85-C-5133-03

OUTCOME
(To be completed for all subjects)

☒	Protocol completed	22Aug86 ddmmmyy
☐	Premature termination of protocol	_____ ddmmmyy

REASON FOR PREMATURE TERMINATION
(Check appropriate category)

- ☐ Adverse Experience
- ☐ Died During Study
- ☐ Failure To Return For Follow-up
- ☐ Did Not Cooperate
- ☐ Protocol Violation
- ☐ Entry Violation
- ☐ Intercurrent Illness
- ☐ Administrative/Other

If terminated early, explain briefly:

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	M - P F M L	06	PROTOCOL: DAMD 17-85-C-5133 03

CONCOMITANT MEDICATIONS

DRUG NAME	TOTAL DAILY DOSE	DATE STARTED	DATE STOPPED
Heparin flush	100-1000 units	17 Aug 86	19 Aug 86

COMMENTS
(please date and sign all comments)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	A I D F M L	07	PROTOCOL:DAMD 17-85-C-5133-03

PROTOCOL

Study Day	Date ddmmmyy	Procedures
	19Jul86	Screening laboratory
	~~18~~ 16 Jul86	History, Physical Exam
0	19Jul86	Admission
3	21Jul86	Drug Administration

I certify that:

1) I have carefully examined all entries on the data collection forms, consisting of 14 pages, for subject # 07.

2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G Lietman M.D. 16 Dec 86
Investigator's signature dd/mmm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	A J D F M L	07	PROTOCOL:DAMD 17-85-C-5133-03

MEDICAL HISTORY

Date of evaluation 16/Jul/86 (dd mmm yy)

Examiner Brent G. Petty M.D.

Dr. B.G. Petty (print name)

Date of birth 20/Jun/62 (dd mmm yy)

Age 24 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	½ PPD
Alcohol Use		✓	½ pint liquor + 6 pack /d
Recreational Drug Use		✓	1/d (marijuana)
Medications past 2 weeks		✓	multivits
Experimental Drug Exposure		✓	Pharmakinetics
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine(diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	A I D F M L	07	PROTOCOL: DAMD 17-85-C-5133-03

PHYSICAL EXAMINATION
Date 16/Jul/86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
37.0 C	68/min	14/min	122/78	179.5	57.5

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		Mouth - mild pyorrhea
EENT		✓	Ears - Bilat ceruminous Nose - Septum SL → R Throat - lymphoid hyperplasia funduscopic - Perimacular pigmentation
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		Liver edge at RCM
Genitalia			Not Done
Rectal			Not done
Extremities		✓	hyperpigmented birth mark, scratch mark, and scar (R shoulder
Skin		✓	scar (L) upper arm, (L) crown of head, (L) lat. thigh & chest, both hands
Neurologic	✓		

Comments: mild Lumbar scoliosis
"Straight back" thoracic spine

CHEST X-RAY
Date 16/Jul/86

NORMAL	X	ABNORMAL		Describe abnormalities:

Examiner _____

Dr. B.G. Kelly
print name

7.29.86 93

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	A I D F M L	07	PROTOCOL:DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21 Jul 86	0817	N.A	PO	

DOSAGE (total) 60 mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemo-globin %~~
	0	21 Jul 86	0750	0750	*	
	0.25	21 Jul 86	0832	0832	*	
	0.50	21 Jul 86	0847	0847	7.17	
	0.75	21 Jul 86	0902	0902	14.4	
	1.0	21 Jul 86	0917	0917	35.9	
	1.25	21 Jul 86	0932	0932	73.2	
	1.50	21 Jul 86	0947	0947	85.7	
	2.0	21 Jul 86	1017	1017	116.	
	2.5	21 Jul 86	1047	1047	102.	
	3.0	21 Jul 86	1117	1117	94.1	
	3.5	21 Jul 86	1147	1147	94.9	
	4.0	21 Jul 86	1217	1217	102.	
	5.0	21 Jul 86	1317	1317	91.4	
	6.0	21 Jul 86	1417	1417	89.7	
	8.0	21 Jul 86	1617	1617	88.4	
	10.0	21 Jul 86	1817	1817	64.6	
	12.0	21 Jul 86	2017	2017	66.0	

29.86 JB

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	A I D F M L	07	PROTOCOL: DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0817	N.A.	PO	

DOSAGE (total) 60mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemoglobin~~ *
	24.0	22Jul86	0817	0817	31.0	
	36.0	22Jul86	2017	2017	17.0	
	48.0	23Jul86	0817	0820	11.3	
	60.0	23Jul86	2017	2135	*	
	72.0	24Jul86	0817	0822	*	
	84.0	24Jul86	2017	2022	*	
	96.0	25Jul86	0817	0820	*	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	A (F) I (M) D (L)	07	PROTOCOL: DAMD 17-85-C-5133-03

URINE CONCENTRATIONS

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0817	N.A.	PO	

DOSAGE (total) 60 mg

URINE CONCENTRATIONS

Sample No.	Scheduled Collection Time (hours)	Start Collection		End Collection		Total Volume (ml)	[WR6026] mg
		ddmmmyy	0-2400	ddmmmyy	0-2400		
U01	-24 TO -12	20Jul86	0800	20Jul86	2000	1410	—
U02	-12 TO 0	20Jul86	2000	21Jul86	0805	1500	0
U03	0 TO 12	21Jul86	0805	21Jul86	2000	960	0.5[illegible]
U04	12 TO 24	21Jul86	2000	22Jul86	0800	1300	0.429
U05	24 TO 36	22Jul86	0800	22Jul86	2000	1605	0.[illegible]
U06	36 TO 48	22Jul86	2000	23Jul86	0800	1505	0.16[illegible]
U07	48 TO 60	23Jul86	0800	23Jul86	2000	1095	0.04[illegible]
U08	60 TO 72	23Jul86	2000	24Jul86	0805	1195	0.0239
U09	72 TO 84	24Jul86	0805	24Jul86	2000	1565	0
U10	84 TO 96	24Jul86	2000	25Jul86	0820	1460	0

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	A I D F M L	07	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Screen -	Predrug 1	Predrug 2	Postdrug 4	Postdrug 5	Day
	14Jul86 ddmmmyy	19Jul86 ddmmmyy	21Jul86 ddmmmyy	22Jul86 ddmmmyy	23Jul86 ddmmmyy	Date
NA:135-148 MEQ/L	145	145	139	140	139	
K:3.5-5.0 MEQ/L	4.5	4.7	4.4	4.4	4.4	
CL:96-109 MEQ/L	109	105	110	106	106	
CO2:24-30 MEQ/L	24	20	24	19	18	
SUN:12-25 MG/DL	7	6	9	9	11	
CREAT:0.4-1.5 MG/DL	1.0	1.1	0.9	1.0	1.1	
GLU:70-115 MG/DL	85	66	86	87	80	
T.BILI:0.3-1.2MG/DL	0.3	0.2	0.2	0.3	0.3	
D.BILI:0.1-0.4MG/DL	0.1	0.1	0.0	0.1	0.1	
CA:9.0-11.0 MG/DL	—	9.7	10.0	9.2	9.5	
PO4:3.0-4.5 MG/DL	3.5	4.6	4.6	4.9	5.0	
URIC A:4.2-8.8MG/DL	5.0	7.0	4.2	4.9	4.5	
T. PROT:6.0-8.5G/DL	6.8	7.2	6.5	6.4	7.0	
ALB.:3.2-5.3 G/DL	4.6	4.7	4.2	4.4	4.4	
AST:0-35 IU/L	30	24	37	36	57	
ALT:0-30 IU/L	26	19	28	26	36	
ALK PHOS:0-95 IU/L	51	56	48	54	60	
CHOL:151-268 MG/DL	141	141	160	148	176	
LDH:0-200 IU/L	126	186	131	190	177	
CPK:0-160 U/L(male)	136	186	83	73	64	
TG:20-190 MG/DL	84	ND	119	114	107	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	A I D F M L	07	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Postdrug 7					Day
	25Jul86	08Aug86	21Aug86	10Sep86	_____	Date
	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
NA:135-148 MEQ/L	140	ND		ND		
K:3.5-5.0 MEQ/L	4.3					
CL:96-109 MEQ/L	102					
CO2:24-30 MEQ/L	28					
SUN:12-25 MG/DL	9	6	4			
CREAT:0.4-1.5 MG/DL	1.0	1.1	1.0			
GLU:70-115 MG/DL	60	105	93			
T.BILI:0.3-1.2MG/DL	0.5	0.8	0.3			
D.BILI:0.1-0.4MG/DL	0.1	0.1	0.0			
CA:9.0-11.0 MG/DL	10.1	10.1	9.7			
PO4:3.0-4.5 MG/DL	4.3	3.3	3.6			
URIC A:4.2-8.8MG/DL	4.9	5.4	6.4			
T. PROT:6.0-8.5G/DL	7.0	6.6	6.6			
ALB.:3.2-5.3 G/DL	4.7	4.4	4.4			
AST:0-35 IU/L	39	56	31	35		
ALT:0-30 IU/L	63	27	39	23		
ALK PHOS:0-95 IU/L	48	70	61	ND		
CHOL:151-268 MG/DL	191	166	178			
LDH:0-200 IU/L	150	ND	ND			
CPK:0-160 U/L(male)	108					
TG:20-190 MG/DL	96					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	A I D F M L	07	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Screen -	Predrug 1	Predrug 3	Postdrug 4	Postdrug 5	Day
		14Jul86	19Jul86	21Jul86	22Jul86	23Jul86	Date
		ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
WBC	4500-11000	4500	5600	5500	6300	5700	
RBC	4.50-5.90	4.32	4.31	4.22	4.31	4.51	
Hgb	13.9-16.3	15.8	15.4	15.9	15.7	16.2	
PCV	41.0-53.0	45.5	45.6	45.4	46.4	47.8	
Plt	150-350	215	339	300	293	276	
Bands	2-6%	3	5	2	6	3	
Polys	31-76%	57	50	53	51	50	
Eos	1-4%	0	0	2	4	0	
Bas		0	0	0	0	1	
Lymphs	24-44%	38	40	38	30	32	
Atyp Lym		0	0	0	0	2	
Monos	2-11%	2	5	5	9	12	
Other		∅	∅	∅	∅	∅	
Methem.		14Jul86 0.4		0.2/0.3	0.0	0.0	
G-6-PD	7.4-9.4	8.2					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	A I D F M L	07	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

		Postdrug 7					Day
TEST	NORMAL	25Jul86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	Date
WBC	4500-11000	8000					
RBC	4.50-5.90	4.41					
Hgb	13.9-16.3	16.0					
PCV	41.0-53.0	46.7					
Plt	150-350	248					
Bands	2-6%	1					
Polys	31-76%	61					
Eos	1-4%	~~30~~ 30					
Bas		1					
Lymphs	24-44%	30					
Atyp Lym		0					
Monos	2-11%	7					
Other		0					
methem		0.3					
G-6-PD	7.4-9.4						

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	A I D F M L	07	PROTOCOL: DAMD 17-85-C-5133-03

URINALYSIS VALUES

Laboratory: JOHNS HOPKINS HOSPITAL

		Screen –	Predrug 1	4	Postdrug 5	7
		16Jul86 ddmmmyy	19Jul86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	25Jul86 ddmmmyy
Sp. Gr.		1.016	1.008			1.006
pH		5.0	6.0			6.0
Protein		neg	neg			neg
Glucose		neg	neg			neg
Ketones		neg	neg			neg
Bili.		neg	neg			neg
Occ. Bld.		neg	neg			neg
Cast/lpf		0	ND			0
WBC/hpf		0				0
RBC/hpf		0				0
Epi./hpf		2-4				0-1
Crys/hpf		0				0
Bact/hpf		many				0

ELECTROCARDIOGRAM

Date ddmmmyy	Time 0-2400	NORMAL check	ABNORMAL check	Describe abnormalities
Screen 16Jul86 21Jul86	0645	✓ ✓		
21Jul86	1202	✓		
22Jul86		✓		
23Jul86	0907	✓		
25Jul86		✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	A I D F M L	07	PROTOCOL:DAMD 17-85-C-5133-03

ADVERSE EXPERIENCES

check if none occurred ☐

#	ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
1	Middle ear fluid	21 Jul 86 dd mmm yy (0-2400)	10 Sep 86 dd mmm yy (0-2400)	☒ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☒ DEF. NOT ☐ UNKNOWN	☒ None ☐ Treatment ☐ Stop test drug
2	Middle ear fluid	23 Jul 86 dd mmm yy (0-2400)	05 Aug 86 dd mmm yy (0-2400)	☒ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☒ DEF. NOT ☐ UNKNOWN	☐ None ☐ Treatment ☐ Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	A L D F M L	07	PROTOCOL: DAMD 17-85-C-5133-03

OUTCOME
(To be completed for all subjects)

☒	Protocol completed	25Jul86 ddmmmyy
☐	Premature termination of protocol	_____ ddmmmyy

REASON FOR PREMATURE TERMINATION
(Check appropriate category)

- ☐ Adverse Experience
- ☐ Died During Study
- ☐ Failure To Return For Follow-up
- ☐ Did Not Cooperate
- ☐ Protocol Violation
- ☐ Entry Violation
- ☐ Intercurrent Illness
- ☐ Administrative/Other

If terminated early, explain briefly:

_____

_____

_____

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	A I D F M L	07	PROTOCOL: DAMD 17-85-C-5133 03

CONCOMITANT MEDICATIONS

DRUG NAME	TOTAL DAILY DOSE	DATE STARTED	DATE STOPPED
heparin flush	100-1000 units	21 Jul 86	24 Jul 86

COMMENTS
(please date and sign all comments)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	C L H F M L	08	PROTOCOL:DAMD 17-85-C-5133-03

PROTOCOL

Study Day	Date ddmmmyy	Procedures
3	16Jul86	Screening laboratory
	17Jul86	History, Physical Exam
0	19Jul86	Admission
3	21Jul86	Drug Administration

I certify that:

1) I have carefully examined all entries on the data collection forms, consisting of 14 pages, for subject #08.

2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Robert G Kelly M.D. 16/Dec/86
Investigator's signature dd/mmm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	C L H F M L	08	PROTOCOL:DAMD 17-85-C-5133-03

MEDICAL HISTORY

Date of evaluation 17/Jul/86 (dd mmm yy)

Examiner Brent G Petty, MD

Dr. B.G. Petty (print name)

Date of birth 25/Oct/51 (dd mmm yy)

Age 34 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	½ PPD
Alcohol Use		✓	2-6 pks / weekend
Recreational Drug Use	✓		MJ 1 yr ago
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	ceftriaxone, tobramycin
Blood or plasma donor		✓	2 yrs ago
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine(diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	GC Rx'd c PCN - 1980
Musculoskeletal	✓		
Neuropsychiatric	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	C L H F M L	08	PROTOCOL:DAMD 17-85-C-5133-03

PHYSICAL EXAMINATION
Date 17 Jul 86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
36.7 C	60/min	10/min	128/82	178.0	76.0

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT	✓		mouth - fair dental hygiene eyes - SL deep + wide optic cups
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia	✓		Not done
Rectal			Not done
Extremities	✓		
Skin		✓	Scar dorsal (R hand Scar (L) lateral eye
Neurologic	✓		

CHEST X-RAY
Date 17 Jul 86

NORMAL	X	ABNORMAL		Describe abnormalities:

Examiner [signature]
Dr B.G. Pethy
print name

7.28.86 B

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	C L H F M L	08	PROTOCOL: DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21 Jul 86	0820	N.A.	PO	

DOSAGE (total) 60 mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	~~Methemoglobin~~ %
	0	21 Jul 86	0805	0805	*	
	0.25	21 Jul 86	0835	0835	*	
	0.50	21 Jul 86	0850	0850	7.63	
	0.75	21 Jul 86	0905	0905	13.2	
	1.0	21 Jul 86	0920	0920	14.2	
	1.25	21 Jul 86	0935	0935	16.3	
	1.50	21 Jul 86	0950	0950	45.3	
	2.0	21 Jul 86	1020	1020	65.2	
	2.5	21 Jul 86	1050	1050	60.5	
	3.0	21 Jul 86	1120	1120	64.4	
	3.5	21 Jul 86	1150	1150	47.3	
	4.0	21 Jul 86	1220	1220	66.9	
	5.0	21 Jul 86	1320	1320	62.0	
	6.0	21 Jul 86	1420	1420	54.2	
	8.0	21 Jul 86	1620	1620	30.8	
	10.0	21 Jul 86	1820	1821	27.6	
	12.0	21 Jul 86	2020	2021	19.7	

7.28.86 JB

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	C L H F M L	08	PROTOCOL: DAMD 17-85-C-5133-03

MEDICATION RECORD

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0820	NA	PO	

DOSAGE (total) 60 mg

* Below Assay Sensitivity

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[WR6026]	Methemoglobin -%
	24.0	22Jul86	0820	0820	8.43	
	36.0	22Jul86	2020	2020	6.60	
	48.0	23Jul86	0820	0827	*	
	60.0	23Jul86	2020	2145	*	
	72.0	24Jul86	0820	0820	*	
	84.0	24Jul86	2020	2026	*	
	96.0	25Jul86	0820	0820	*	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	C L H F M L	08	PROTOCOL: DAMD 17-85-C-5133-03

URINE CONCENTRATIONS

STUDY: WR6026

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	21Jul86	0820	N.A.	PO	

DOSAGE (total) 60mg

URINE CONCENTRATIONS

Sample No.	Scheduled Collection Time (hours)	Start Collection		End Collection		Total Volume (ml)	[WR6026] mg/ml
		ddmmmyy	0-2400	ddmmmyy	0-2400		
U01	-24 TO -12	20Jul86	0800	20Jul86	2000	1285	
U02	-12 TO 0	20Jul86	2000	21Jul86	0800	1920	0
U03	0 TO 12	21Jul86	0800	21Jul86	2000	1135	0.21[illegible]
U04	12 TO 24	21Jul86	2000	22Jul86	0800	1525	0.131506
U05	24 TO 36	22Jul86	0800	22Jul86	2000	2590	0.042943
U06	36 TO 48	22Jul86	2000	23Jul86	0800	1615	0.019099
U07	48 TO 60	23Jul86	0800	23Jul86	2000	2600	0.004174
U08	60 TO 72	23Jul86	2000	24Jul86	0800	1890	0.005197
U09	72 TO 84	24Jul86	0800	24Jul86	2000	1860	0
U10	84 TO 96	24Jul86	2000	25Jul86	0800	1970	0
							✓

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	C L H F M L	08	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Screen -	Predrug 1	Predrug 2	Postdrug 4	Postdrug 5	Day
	16Jul86 ddmmmyy	19Jul86 ddmmmyy	21Jul86 ddmmmyy	23Jul86 ddmmmyy	25Jul86 ddmmmyy	Date
NA:135-148 MEQ/L	143	140	136	140	140	
K:3.5-5.0 MEQ/L	4.5	4.6	4.0	4.6	4.3	
CL:96-109 MEQ/L	107	105	101	108	105	
CO2:24-30 MEQ/L	28	20	26	18	2-	
SUN:12-25 MG/DL	9	9	12	14	16	
CREAT:0.4-1.5 MG/DL	0.9	0.9	0.8	0.7	0.8	
GLU:70-115 MG/DL	101	64	70	87	77	
T.BILI:0.3-1.2MG/DL	0.5	0.2	0.5	0.2	0.3	
D.BILI:0.1-0.4MG/DL	0.2	0.0	0.1	0.0	0.0	
CA:9.0-11.0 MG/DL	9.5	9.8	9.9	9.2	9.9	
PO4:3.0-4.5 MG/DL	3.4	3.6	3.5	3.5	3.8	
URIC A:4.2-8.8MG/DL	6.7	7.2	5.9	7.4	7.2	
T. PROT:6.0-8.5G/DL	6.9	6.9	7.3	6.5	7.1	
ALB.:3.2-5.3 G/DL	4.7	4.8	4.8	ND	4.8	
AST:0-35 IU/L	21	17	21	16	18	
ALT:0-30 IU/L	18	23	11	13	12	
ALK PHOS:0-95 IU/L	33	34	33	30	31	
CHOL:151-268 MG/DL	217	238	154	209	275	
LDH:0-200 IU/L	~~148~~ 113	133	189	155	129	
CPK:0-160 U/L(male)	116	98	85	79	78	
TG:20-190 MG/DL	377	ND	275	144	134	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	C L H F M L	08	PROTOCOL:DAMD 17-85-C-5133-03

CHEMISTRY VALUES
Laboratory:JOHNS HOPKINS HOSPITAL

TEST:NORMAL	Postdrug 7 Day 25Jul86 ddmmmyy	15Aug86 ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
NA:135-148 MEQ/L	140	ND			
K:3.5-5.0 MEQ/L	4.0	ND			
CL:96-109 MEQ/L	103	ND			
CO2:24-30 MEQ/L	21	ND			
SUN:12-25 MG/DL	14	9			
CREAT:0.4-1.5 MG/DL	0.9	1.0			
GLU:70-115 MG/DL	75	129			
T.BILI:0.3-1.2MG/DL	(Lab Accident) ND	1.4			
D.BILI:0.1-0.4MG/DL	ND	0.1			
CA:9.0-11.0 MG/DL	ND	9.9			
PO4:3.0-4.5 MG/DL	ND	3.7			
URIC A:4.2-8.8MG/DL	ND	8.2			
T. PROT:6.0-8.5G/DL	ND	7.2			
ALB.:3.2-5.3 G/DL	ND	4.9			
AST:0-35 IU/L	ND	31			
ALT:0-30 IU/L	ND	19			
ALK PHOS:0-95 IU/L	ND	43			
CHOL:151-268 MG/DL	ND	195			
LDH:0-200 IU/L	192	ND			
CPK:0-160 U/L(male)	88	ND			
TG:20-190 MG/DL	185	ND			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	C L H F M L	08	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Screen -	Predrug 1	Predrug 3	Postdrug 4	Postdrug 5	Day
		16Jul86	19Jul86	21Jul86	22Jul86	23Jul86	Date
		ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
WBC	4500-11000	6900	8000	8000	8300	7200	
RBC	4.50-5.90	5.16	5.14	5.27	4.79	5.01	
Hgb	13.9-16.3	14.6	14.4	15.2	13.6	14.4	
PCV	41.0-53.0	45.5	43.5	45.5	41.4	43.7	
Plt	150-350	262	295	302	290	294	
Bands	2-6%	0	4	8	2	8	
Polys	31-76%	~~80~~ 65	47	41	58	49	
Eos	1-4%	3	1	2	2	2	
Bas		0	0	1	0	0	
Lymphs	24-44%	32	48	40	34	37	
Atyp Lym		0	0	0	0	1	
Monos	2-11%	0	0	8	4	3	
Other		0	0	0	0	0	
Methem:	0.0 - 1.5	17Jul86 0.3		0.0 ~~0.2~~	0.4	0.1	
G-6-PD	7.4-9.4	7.3					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	C L H F M L	08	PROTOCOL:DAMD 17-85-C-5133-03

HEMATOLOGY VALUES
Laboratory: JOHNS HOPKINS HOSPITAL

TEST	NORMAL	Postdrug 7 Day 25Jul86 Date ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy	_____ ddmmmyy
WBC	4500-11000	8700				
RBC	4.50-5.90	5.17				
Hgb	13.9-16.3	14.4				
PCV	41.0-53.0	44.0				
Plt	150-350	303				
Bands	2-6%	0				
Polys	31-76%	48				
Eos	1-4%	1				
Bas		0				
Lymphs	24-44%	43				
Atyp Lym		1				
Monos	2-11%	7				
Other		0				
methem	0.0-1.5	0.3				
G-6-PD	7.4-9.4					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	C L # (F M L)	08	PROTOCOL: DAMD 17-85-C-5133-03

URINALYSIS VALUES

Laboratory: JOHNS HOPKINS HOSPITAL

	Screen –	Predrug 1		4	Postdrug 5	7
	17Jul86 ddmmmyy	19J_12 ddmmmyy		_____ ddmmmyy	_____ ddmmmyy	25Jul86 ddmmmyy
Sp. Gr.		1.003	1.012			1.008
pH		6.0	6.0			6.0
Protein		Neg	Neg			Neg
Glucose		Neg	Neg			Neg
Ketones		Neg	Neg			Neg
Bili.		Neg	Neg			Neg
Occ. Bld.		Neg	Neg			Neg
Cast/lpf		0	NP			0
WBC/hpf		0-1				0
RBC/hpf		0				0
Epi./hpf		0				0
Crys/hpf		0				0
Bact/hpf		0				0

ELECTROCARDIOGRAM

Date ddmmmyy	Time 0-2400	NORMAL check	ABNORMAL check	Describe abnormalities
17Jul86	1446	✓		
19Jul86	0715	✓		
20Jul86	1137	✓		
21Jul86	0917	✓		
23Jul86	0910	✓		
25Jul86	0844	✓		

screen

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND:WR6026
LIETMAN	C L H F M L	08	PROTOCOL:DAMD 17-85-C-5133-03

ADVERSE EXPERIENCES

check if none occurred ☒

#	ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
		__ __ __ dd mmm yy _____ (0-2400)	__ __ __ dd mmm yy _____ (0-2400)	☐ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☐ DEF. NOT ☐ UNKNOWN	☐ None ☐ Treatment ☐ Stop test drug
#		__ __ __ dd mmm yy _____ (0-2400)	__ __ __ dd mmm yy _____ (0-2400)	☐ Mild ☐ Mod ☐ Sev	☐ DEF. ☐ PROB. ☐ POSS. ☐ DEF. NOT ☐ UNKNOWN	☐ None ☐ Treatment ☐ Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	C L H F M L	08	PROTOCOL:DAMD 17-85-C-5133-03

OUTCOME
(To be completed for all subjects)

☒	Protocol completed	25Jul86 ddmmmyy
☐	Premature termination of protocol	_____ ddmmmyy

REASON FOR PREMATURE TERMINATION
(Check appropriate category)

- ☐ Adverse Experience
- ☐ Died During Study
- ☐ Failure To Return For Follow-up
- ☐ Did Not Cooperate
- ☐ Protocol Violation
- ☐ Entry Violation
- ☐ Intercurrent Illness
- ☐ Administrative/Other

If terminated early, explain briefly:

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND: WR6026
LIETMAN	C L H F M L	08	PROTOCOL: DAMD 17-85-C-5133 03

CONCOMITANT MEDICATIONS

DRUG NAME	TOTAL DAILY DOSE	DATE STARTED	DATE STOPPED
heparin flush	100 1000 units	3 Jul 86	05 Jul 86

COMMENTS
(please date and sign all comments)

APPENDIX F
Distribution List

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